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# Further Studies of the Cardiodynamics of Experimental Intraventricular Communications

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This communication deals with the altered ventricular dynamics occasioned by temporary opening of a large artificial interventricular shunt. Since the left ventricular discharge into the right ventricle begins some time after ejection of blood into the aorta, the left ventricle assists the right in propelling larger quantities of blood through the pulmonary circuit. This late systolic flow through a shunt causes characteristic deformations of central arterial pressure pulses and a midsystolic murmur similar to those observed in several clinical cases.

WHILE considerable progress has been made in the understanding of abnormal circulatory and respiratory states resulting from congenital cardiac defects, knowledge of the basic changes of cardiac behavior is still rather meager. A start in evaluating the compensatory mechanisms brought about by interventricular septal defects was made by Dillon and Schreiber.[1] Through analysis of pressure pulses recorded from the right and left ventricles, inferences were drawn regarding the important roles that the *right ventricle* plays both in increasing the return to the left heart and in reducing the leak through the interventricular defect by a rise of the right ventricular systolic pressure.

This study was undertaken to confirm their conclusions by use of methods which interfered less with the normal action of the ventricles and to extend their observations by analyzing more in detail how the *left ventricle* operates in the presence of an interventricular communication. For this purpose an external shunt that could be opened and closed at will was established as described by Dillon and Schreiber.[1] However, the shunt was not fixed by the rigid clamps necessary for registration of ventricular pressures in their experiments. Hence, a more normal state of cardiac contraction could be maintained and leakage of blood around the cannulae, with subsequent need for repeated transfusion of blood, was avoided. Simultaneously recorded pressure pulses from the pulmonary artery and aorta were studied to provide information regarding modification of the ejection processes by the two ventricles. Right and left atrial pressure recordings were used to evaluate changes in filling and tension on the two sides and the effect of the increased volume of flow on the pulmonary vasculature.

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## METHODS

Dogs anesthetized with morphine and barbital, weighing 13.5 to 18 Kg., were given artificial respiration by tracheal cannula after the chest was opened by a sternum-splitting procedure. Rigid cannulae were inserted into (1) the ascending aorta via the left carotid artery, (2) the pulmonary artery bifurcation via small branches to either left or right upper lobes, and in a few instances (3) the right atrium via the right external jugular vein, and (4) the left atrium via a right upper lobe branch of the pulmonary vein. The incised pericardium was sutured to the chest wall, making a cradle for the heart without embarrassing venous return. Heparin,

5.0 mg.,* was injected intravenously. Previously described[1] L-shaped cannulae 6 to 7 mm. in diameter were inserted through the left and right ventricular myocardium after a scissors incision made by puncture and then spreading the blades. The free ends of the cannulae were connected by short, 7 mm. in diameter, rubber tubing clamped by a hemostat.

All pressures were recorded by modified Gregg optical manometers. To avoid artifacts of pulmonary inflation the lungs were maintained in a position of expiration for a brief period when records were taken. After control records demonstrating satisfactory contours had been obtained, the shunt was opened for varying lengths of time.

Since the magnitude of flow through the artificial shunt necessarily varied in different experiments, it seemed important to establish that it could equal that calculated in clinical cases. For this purpose a supplementary experiment was performed in which right and left ventricular outputs were determined by the Fick method as modified by Brannon et al.[2] Duplicate blood samples were secured from the right atrium, pulmonary artery, and femoral artery, and oxygen content was calculated from duplicate analyses, using the Scholander technic.[3] Oxygen consumption was measured by the positive pressure spirometer described by Harris.[4] The data in table 1 show that three minutes after opening the shunt the aortic ejection volume was near control levels but had declined somewhat by the fifth minute. The data also show 55.3 per cent and 54.1 per cent of the left ventricular minute volume was expelled through the shunt rather than into the aorta, i.e., the pulmonary volume flow was more than double the aortic ejection.

TABLE 1.—*Minute Volumes (cc./min.)*

| | Blood Sample | Pulmonary Artery | Aorta | Shunted blood |
|---|---|---|---|---|
| Control | 1 | 1100 | 1100 | 0 |
| | 2 | 992 | 992 | 0 |
| Shunt open | 1 (open 3 min.) | 2243 | 1002 | 1241 |
| | 2 (open 5 min.) | 1651 | 757 | 849 |
| Shunt closed | 1 | 1043 | 1043 | 0 |
| | 2 | 946 | 946 | 0 |

## RESULTS

Successful experimental conditions were realized in 7 dogs with twenty-one records worthy of analysis. By this is meant that the aortic pressure curves had good forms characteristic of normal systolic discharge and resistance to ejection, and that the systolic pressures were within normal ranges.

Nearly all records were free of artifacts, such as extrasystoles or vibrations caused by manipulation of the shunt, thus permitting the immediate changes following opening and closing of the shunt to be studied in detail. Opening and closing the hemostat on the connecting rubber tubing was found to exert no significant influence per se since the volume change was not more than 0.3 cc.

Typical effects of opening and closing the shunt on the aortic and pulmonary arterial pressure pulses are shown in figure 1. Aortic pressures, including pulse pressure, rapidly fell initially in all experiments when the shunt was opened; the reverse occurred in the pulmonary artery. In time, the aortic pulse pressure increased to a variable extent, and the curve either stabilized at a lower than control level (fig. 1, *B*), or more frequently began to rise to and even above control values. The average initial fall of aortic pressures was 16.4/13.4 mm. Hg; the average rise of the pulmonary artery pressures was 6.3/3.5 mm. Hg. Closure of the shunt caused aortic pressures to reach values as great or greater than control values, invariably higher than the levels just before closing. The pulmonary artery pressure pulse always resumed control levels within a few beats.

Figure 1 also illustrates the marked changes in contour of the aortic and pulmonary artery pressure pulses following the opening of the shunt. The first aortic pressure pulse following opening of the shunt shows a normal early systolic rise; however, the peak pressure is not sustained and pressure falls sharply to the incisural notch. The next aortic pulse shows the same systolic collapse; however, the early systolic rise is slow and resembles that found in adynamic hearts. Within a few beats when the aortic pressure becomes stabilized at a lower than control level, the slope of the early ejection phase has returned to control values. This is shown in figure 1, *B*. The sloping of the curve toward the incisura remains and is a constant feature of pulses recorded from the arch

* Heparin used in these experiments was supplied in part by the Upjohn Company, Kalamazoo, Mich.

of the aorta when the shunt is open. The significance of these changes will be discussed later.

The first pulmonary pressure pulse following opening of the shunt shows a normal early rise of pressure, but the peak pressure is reached .025 second later than in the preceding beat and is sustained until the onset of the incisural notch. The contour compared to control beats is noticeably changed just before attaining the peak pressure when a secondary small but steep rise occurs, and the normal sloping off from the peak pressure to the incisural notch is absent. Succeeding pressure pulses show a series of coarse vibrations near or on the summit (M). These vibrations undoubtedly represent the audible murmur produced by the turbulent flow through the shunt and are best seen in the first beat of figure 1, *B*. The significance of these jogs and murmurs is that they mark the time of maximum turbulent flow through the shunt.

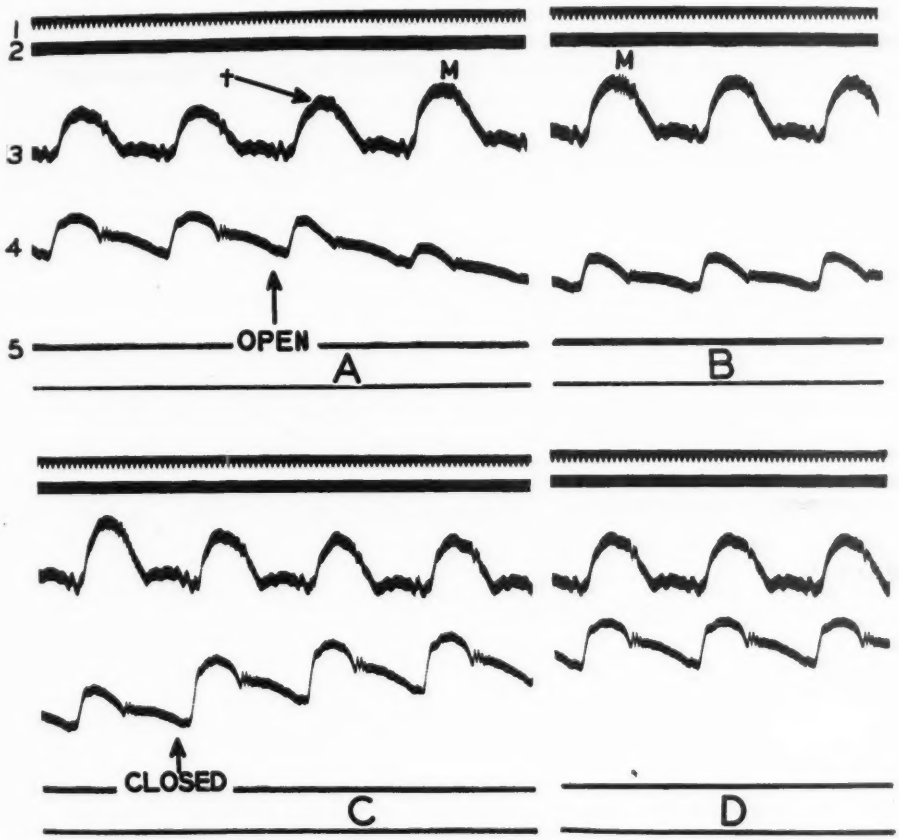


FIG. 1.—Sections of a continuous record. *A*, opening the shunt; *B*, two seconds later; *C*, closing the shunt; *D*, three seconds later. (1) Time .02 second; (2 and 3) pulmonary artery base line and pressure pulse; (4 and 5) aortic pressure pulse and base line. + secondary rise of pressure. M, murmur.

Frequently the aortic pressures returned to or above control values while the shunt was open. Such overcompensation was a temporary phenomenon, being usually observed fifteen seconds after the shunt was opened, but not present fifteen seconds later. It was always

accompanied by an increased pulmonary artery pressure.

During several experiments, optical records were taken of pressures within the right and left atria, particular attention being paid to the instantaneous pressures at the onset of ventricular filling, the so-called "V" point values.[5] The "V" point occurs on the pressure pulse just before the second heart sound, while the A-V valves are still closed, and thus indicate the instantaneous pressure in the atria while they are not contracting or in communication with the ventricles.[6] Either an increased

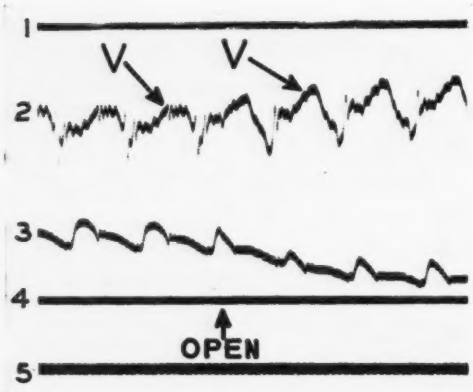


FIG. 2.—Effect of opening shunt on left atrial pressure. (1 and 2) left atrial base line and pressure pulse; (3 and 4) aortic pressure pulse and base line; (5) time .02 second. Further discussion in text.

flow of blood into the atria or a decreased outflow will cause the instantaneous pressures to increase. Opening and closing the shunt had little effect on the right atrial pressures; the "V" point values rose erratically from 2 to 8 mm. of saline. The left atrial curves showed much more striking and consistent changes. Figure 2 shows the directional changes in the left atrial pressure pulse on opening the shunt, and figure 3 shows diagrams of the "V" point values as altered by opening and closing the shunt. The "V" point begins to rise coincident with the first systole after opening the shunt, indicating that an increase of flow into the left atrium begins with this initial beat. A sustained rise of about 30 mm. saline is reached within eight beats. On closing the shunt a temporary rise occurs for two beats, apparently due to resistance to flow into the left ventricle which suddenly has to expel its stroke volume through one instead of two orifices. Thereafter the pressure declines.

*Clinical Correlations.* In animal experiments of this sort it is always desirable to determine how far results of experimental lesions in animals are comparable to those which exist in patients. In both, the magnitude of the shunt flow will naturally vary, for it depends on the dynamic balances of pressures as well as on the size of the canal. Although comparisons are difficult, it is a fair conclusion that the shunt flows created in our experiments—nearly 50

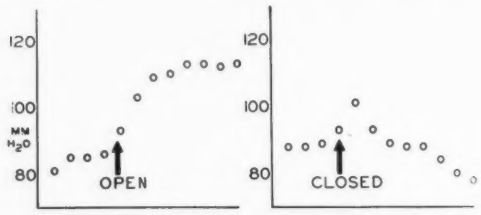


FIG. 3.—Effect of opening and closing shunt on left atrial "V" point values. Each dot represents one beat.

per cent of the left ventricular stroke volume in one test—equaled those present in most congenital septal defects.

Although human interventricular septal defects are usually of congenital origin, they also occur as a result of perforation of a septal myocardial infarct[7, 8] or traumatic rupture.[9] Indeed, in these two acquired conditions, if the defect were to develop with sufficient size and speed, the cardiodynamics would be very similar to opening the experimental shunt. Clinical reports of perforation of septal infarct have emphasized the acute onset of dyspnea[7] and lowered blood pressure[8] coincident with the manifestation of a systolic murmur. The dyspnea, judging from our experiments, may be due in part to active congestion of the lungs brought about by the increased pulmonary flow before left ventricular compensation takes place. Since these patients routinely have hypertensive vascular disease and coronary

atherosclerosis, left ventricular compensation is often incomplete, leading to passive pulmonary congestion.

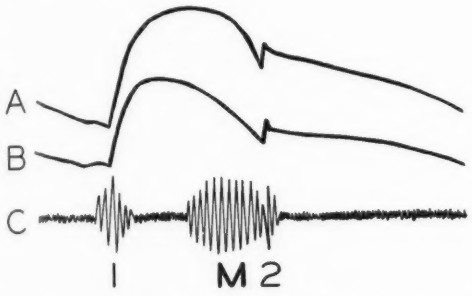


FIG. 4.—Diagrams of aortic pressure pulses and of phonocardiogram. *A*, normal aortic pressure pulse; *B*, aortic pressure pulse after shunt is opened; *C*, phonocardiogram showing heart sounds (1 and 2) and systolic murmur (M).

of the central artery pressure pulse contour. Experimentally, analysis of photographically enlarged pulmonary artery pressure pulses reveals a murmur during the latter half of systole which, if it were recorded phonocardiographically, would appear as in figure 4, *C*. The central artery pulse shows a rapid rise to a summit and a late systolic decline (fig. 4, *B*) instead of the normal typical contour (*A*).

A review of the clinical literature reveals a divergence of opinion as to the time of the murmur during systole. Some authors, on the basis of clinical impression,[10] state that the murmur occurs after the first sound or even in midsystole.[11] However, others[12] state that it is coincident with the first heart sound. Levine and Harvey[13] have recently described the murmur as systolic in time, but a review of their phonocardiograms shows the murmur to be

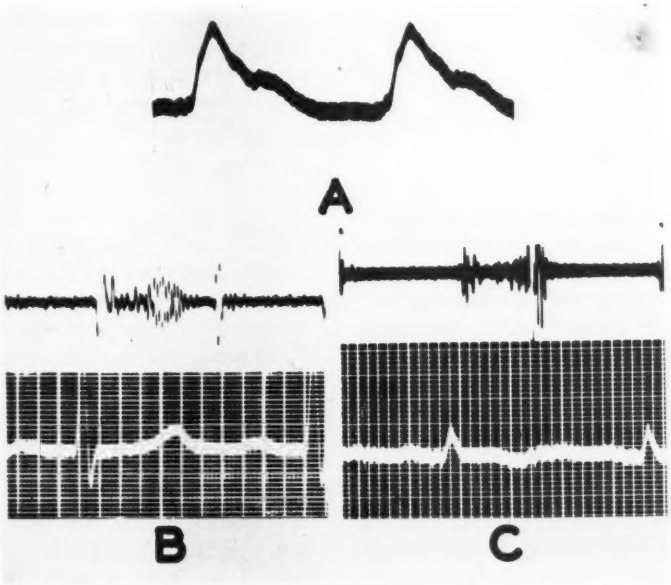


FIG. 5.—Records from clinical cases of interventricular septal defects. *A*, subclavian pressure pulse; *B* and *C*, phonocardiograms of murmur.

Two additional ways suggest themselves of comparing our data from temporary experimental lesions with those in patients, applying equally well to congenital and acquired lesions. These are (1) the timing of the murmur caused by the shunted blood and, (2) the alteration

most intense at mid- or in late systole. Phonocardiograms by other authors are unsatisfactory.

Examination of a limited number of heart sounds taken routinely at Lakeside Hospital by one of us (H. F.) revealed a midsystolic

placement of the murmur in 4 cases, as illustrated in figure 5, *B* and *C*. Also, subclavian pulses recorded from one of the patients with proper technic (fig. 5, *A*) displayed a wave form similar to that obtained from the aorta in our experiments. We realize that a larger number of observations are required before it can be decided that all types and locations of human septal defects duplicate the dynamic conditions which were produced experimentally. However, the few similar clinical data available suffice to formulate a tentative concept of how the ventricles adapt themselves to an interventricular shunt and thus not infrequently maintain a reasonably efficient circulation over a period of many years.

## Discussion of the Dynamics of Interventricular Shunts

On opening an interventricular shunt, a considerable fraction of the left ventricular stroke volume passes into the right ventricle instead of being expelled into the aorta. This shunted volume added to the normal venous return immediately augments the volume ejected from the right ventricle into the lungs. The increased pulmonary flow passes into the left heart, enabling the left ventricle to increase its stroke volume and to eject greater volumes of blood into the aorta and right ventricle combined. The dynamic mechanisms whereby larger volumes are delivered by the right heart to the left so that the latter in turn can eject larger stroke volumes through divided circuits can be deduced from our experiments. We have shown that when a shunt is established between the right and left ventricles the immediate effect consists of a fall in aortic and a rise of pulmonary arterial pressures. Even when as much as half of the left ventricular stroke volume passes through the shunt, the dynamic conditions are such that the aorta receives its half demonstrably earlier than does the shunt; in fact, significant flow through the shunt indicated by onset of a murmur does not start until right ventricular ejection is well under way. Coincident with establishment of the shunt flow, the aortic ejection diminishes, causing the systolic decline of aortic pressure.

Dillon and Schreiber[1] found a definite increase in initial diastolic tension in the right ventricle and properly inferred that the greater diastolic stretch causes the right ventricle to contract with greater strength. They concluded that this is the compensating mechanism by which the right ventricle delivers the necessary larger volumes of blood through the pulmonary vessels to the left heart. While we agree that this mechanism is concerned, our evidence indicates that the whole strain involved in delivery of larger stroke volumes does not fall upon the right ventricle. The left ventricle, by ejecting a considerable stroke volume to the right ventricle some time after ejection has begun, directly shares in supplying part of the force necessary to move larger volumes through the pulmonary vessels. The operation of this left ventricular mechanism is well illustrated in figure 1 from an experiment in which the shunt was opened late in diastole. The succeeding pressure wave in the pulmonary artery begins to rise with a normal slope. But just prior to reaching the systolic peak there is a second small but sharp rise at the arrow, +, increasing the systolic pressure above the control values, and this maximal pressure is well sustained until the incisural notch. As noted in the following beats, this pressure increase takes place during the same interval of systole that the murmur appears. Thus, the blood ejected via the shunt into the right heart is the basis of this secondary pressure increase. The initial systolic rise of the succeeding pulmonary artery pressure pulse is definitely steeper, indicating a more forceful right ventricular contraction brought about by increase of diastolic length. The murmur near the summit and the sustained systolic peak are evidence that the left ventricular component continues to exert its effect. In short, mechanisms by which pulmonary arterial pressures and blood flow increase depend both on increasing the right ventricular diastolic stretch and on the contractile power of the left ventricle.

If a shunt is allowed to remain open, aortic pressures often recover nearly to or occasionally above control levels, indicating that the total

stroke volume has increased sufficiently so that half of this discharge nearly equals its total normal discharge into the aorta. Before this state is attained, a considerable degree of active pulmonary congestion takes place, involving a transfer of a volume of blood from the systemic to the pulmonary circulation. This active congestion is evidenced by both left atrial and aortic pressure changes. The left atrial pressure stays increased when the shunt is opened and for a few beats when it is closed. This latter event occurs despite a normal venous return to the right heart being ejected into the lungs and shows that flow from the lungs to the left atrium is greater than control volumes. Of a similar nature is the coincident temporary rise of aortic pressures, including pulse pressure, above control values when the shunt is closed as the congested blood in the lungs is being dissipated. The rapidity with which these changes take place is striking. Pressures in the right ventricle and pulmonary artery fall coincident with the *first systole* after the shunt is closed; those in the left atrium by the sixth beat. The initial adjustment brought about by by the opening and closing of the shunt as manifested by the aortic, pulmonary artery, and atrial pressure pulses are routinely completed by the tenth beat.

It will be noted that the altered dynamics of cardiac behavior during existence of an interventricular shunt depend on the asynchronicity of left ventricular ejection into the aorta and right ventricle. The reason why priority of ejection occurs over the normal outflow tract is not wholly clear. The lateral placement of a septal shunt is certainly not the only factor concerned, for a similar delay has been shown to occur in mitral regurgitation[14] and in tricuspid insufficiency[15] in which a basal leak exists adjacent to the aortic or pulmonary orifices. In all of these conditions such priority of aortic ejection only occurs when a vigorous ventricular contraction and brusque elevation of tension during isometric contraction exist. When for any reason the ventricular beats become weakened, the flow occurs simultaneously and even preferentially through shunts or A-V valvular leaks, with resulting diminution in aortic discharge and development of circulatory failure. Apparently, the so-called "outflow tract of the ventricles" is a dynamic condition rather than a morphological arrangement.

## Summary

In order to evaluate more exactly the roles of the left ventricle and pulmonary vasculature in the presence of an interventricular defect, an external interventricular communication was established in anesthetized dogs. Optical records were taken from the ascending aorta, pulmonary artery, and right and left atria by calibrated manometers of adequate efficiency.

Opening the shunt caused an immediate fall of aortic pressures and a rise of pulmonary artery and left atrial pressures. Right atrial pressures were unaffected. Varying degrees of aortic pressure compensation occurred. Closing the shunt caused, in general, effects opposite to opening.

The following conclusions were drawn: (1) Pulmonary artery (and right ventricular) systolic pressure is increased both by flow from the left ventricle into the semirigid right ventricle and by increased right ventricular diastolic length. (2) The pulmonary vasculature transmits practically instantaneously pressure-volume changes in the pulmonary artery as far as the left atrium. Active pulmonary congestion results from the increased right ventricular ejection. (3) Most of the flow through the shunt occurs after left ventricular ejection is well established. (4) Compensation of aortic pressures depends upon increasing volumes of blood returning to the left heart from the lungs.

The experimental data were correlated with clinical findings. Attention was drawn to the timing of the murmur, the increased ventricular output, and the diagnostic significance of recording the subclavian pressure pulse in patients with congenital ventricular septal defects. The similarity to perforation (following infarction or trauma) of human interventricular septa was mentioned.

## Acknowledgment

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# Commissurotomy for Mitral Stenosis

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The term "mitral commissurotomy" has been suggested to designate a procedure in which the individual anatomic leaflets of the stenotic mitral valve are surgically separated. By incising the angles or commissures of the mitral slit ("fish-mouth") a considerable degree of valve function can be re-established without the production of additional significant regurgitation. Commissurotomy, as described below, was performed in 8 cases of advanced mitral stenosis. Results in 5 were most satisfactory. There were three deaths early in our experience during the period when our technic was being perfected. (Noted in addendum are 22 cases undergoing the operation since this article was submitted for publication, and bringing the total series to 30.)

IT WAS inevitable that the many recent advances in cardiac diagnosis and surgery would shortly foster invasion of the heart chambers. Of equal certainty was the fact that chronic valvular disease of the heart, the most common intracardiac disorder, would be among the first conditions subjected to surgical consideration. That valvular disease is common and found universally is well known. Indeed, White[1] has estimated that 0.5 to 1.0 per cent of the community at large is affected, particularly in those areas where rheumatic fever is endemic, as in northeastern United States and northern Europe. The great majority of persons afflicted with rheumatic heart disease (up to 85 per cent) develop some degree of deforming valvular disease, the mitral valve being the most common site of involvement. Structural stenosis of the mitral valve is the most deforming end-result of rheumatic infection.

The prognosis of an individual case of mitral stenosis depends upon many factors: the age of the patient, the severity of the lesion, the presence or absence of other valve defects, the presence or absence of additional rheumatic activity, and the condition of the myocardium. The ultimate outcome, however, is almost invariably unfavorable once the stenotic change gives rise to a progressive pattern. Thus, when the diagnosis of early mitral stenosis has been established the cardiologist can picture and predict with considerable accuracy, both by repeated physical examinations and observance of the patient's general condition, the structural and symptomatic phases through which a given case will pass. His treatment will at once be directed toward the prevention of further rheumatic insults and the support of a myocardium which is attempting to maintain adequate systemic circulation in the face of an increasing mechanical stricture. Under such circumstances both the cardiologist and the myocardium are fighting a losing battle. It is little wonder, therefore, that in his deliberations Sir Lauder Brunton[2] as early as 1902 concluded that direct surgical incision of the stenotic valve provided the only logical method of interrupting the relentless chain of events attendant upon progressive mitral stenosis. Support of the myocardium by intelligent therapy has offered the only approach to date, but it is the treatment of the effects of disease rather than the alleviation of its mechanical cause. True, the ideal approach would be the elimination of the causative agent, rheumatic fever. Failing this, however, the correction of its disastrous cicatricial end result seems most logical.

Pursuing this line of reasoning there followed years of sporadic research, both experimental and clinical. Early investigation was concerned with an experimental production of mitral stenosis and insufficiency, providing material for the study of physiologic pressure changes so produced.[3–6] Although even to this day true mitral stenosis simulating the clinical form of the disease has never been duplicated, cicatricial constrictions of the mitral ring have provided a medium for the thorough evaluation of obstructive phenomena upon the pulmonary circulation and right side of the heart.

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By 1929 Cutler and Beck[7] were able to collect 10 cases from the literature in which surgical relief of mitral stenosis had been attempted. These efforts, in the main, had been made by the introduction of punchlike instruments through the myocardium of the left ventricle, blindly engaging upon a mitral valve cusp with the removal of portions of tissue, thereby enlarging the valve orifice but converting a lesion primarily stenotic into one primarily regurgitant. That this was poorly tolerated is evidenced by the fact that only one of 10 patients survived; thus, all surgical attempts fell into disrepute until very recent years. Powers,[8–10] in 1932, demonstrated, again experimentally, that the abrupt conversion of mitral stenosis to mitral regurgitation with its sudden overwhelming increase in pulmonary congestion was responsible for the fatal outcome in patients so treated. This knowledge has prompted more recent investigators to direct their attentions at relief of stenosis by producing either small amounts (controlled) of regurgitation or, more ideally, no additional regurgitation at all. To this end, methods of grafting body tissues into the cardiac chambers to replace deformed valves have been devised but as yet have not been sufficiently perfected to warrant general usage.[11, 12] Thus, since 1929, fourteen additional attempts (not including our own) to relieve mitral stenosis by plastic procedures upon the valve itself have been made.[13–16] Nine of the patients survived the operation but a number have since succumbed as a result of induced, though possibly limited, mitral insufficiency. It is obvious, therefore, that future efforts must be directed at the relief of stenosis without the production of significant regurgitation if long-lasting benefits are to be derived from surgical intervention. The purpose of this communication is to present a method whereby the production of regurgitation has been so minimized as to be not significantly greater than that which inherently exists with all mitral stenosis. Therefore, it is incumbent upon the cardiologist to classify and re-evaluate mitral stenosis on a more exacting physiologic basis so that proper selection of cases for surgical intervention may be forthcoming. For this re-evaluation the work of Cournand and associates[17] and of Bing and his co-workers[18] has been epochal and their methods of thorough study must be more generally applied.

Because of the possible promise of recent surgical developments, one is forced to the conclusion that heart disease as a whole and mitral stenosis in particular must shortly be viewed by the cardiologist from an entirely new perspective. Thus the first signs of developing mitral stenosis demand immediate and repeated evaluation by all possible methods. Careful clinical examination and appraisal by an experienced cardiologist is obviously essential. The cardiologist's armamentarium has long included, in addition to subjective and auscultatory analysis: (1) electrocardiograms and sound recordings; (2) teleoroentgenograms, esophagograms, and fluoroscopy for an estimation of the size of individual heart chambers; (3) exercise tolerance tests; and (4) laboratory data for the detection of rheumatic activity. Such a program has been the standard means of determining the benefit derived from therapeutic measures. To this now must be added procedures for the detection of early physiologic changes. To evaluate cases for surgical intervention, there must be included (5) estimations of cardiac output at rest and with exercise as calculated by ballistocardiography or, more accurately, by utilization of the Fick principle; and (6) determinations of the pulmonary arterial and right ventricular pressures by cardiac catheterization.

Nothing need be said regarding the worth of the first four methods of evaluation. Their importance is unquestioned when carried out by experienced clinicians, even though many minor individual variances may lay stress on one finding rather than another. In many cases, however, the conclusions drawn from this type of evaluation alone may be dependent upon the presence of advanced pathologic changes. Significant pathologic and physiologic changes may well be detected earlier by the recently developed studies (5 and 6 in the preceding paragraph) and point the way toward reconstructive surgery before irreversible changes have occurred.

Certain basic questions must then be answered:

A. Has the primary rheumatic infection completely subsided? What is the probability of recurrence? What effect would recurrence exert upon the valve that has been subjected to operation? While no clear-cut answers can be provided, it seems reasonable that present activity can be detected and that future exacerbations can be prevented in large measure by the established practice of intermittent and long-continued chemotherapy or administration of antibiotics. Certain newer substances such as Compound E recently reported by Hench may prove to be of great value. In spite of precautions, should recurrent activity appear, in all probability further cicatrix would nullify the result of surgical treatment.

B. Is the valvular deformity such that the patient cannot reasonably expect a normal life span with but moderate limitation of activity? Preliminary evaluation of the patient by measuring the pressures within the pulmonary circuit may well be paramount in the making of such a decision. There is a strong suspicion that systolic pressures of 50 mm. Hg within the pulmonary artery may represent the critical level above which the patient must shortly expect serious consequences.

C. Finally, to what point may stenosis be permitted to develop before all reasonable chance of surgical relief is lost? Results obtained to date strongly suggest that in far-advanced cases in patients with fixed, calcified valves, who have or have repeatedly had heart failure, the opportunity for surgical relief has been lost. We believe that both the maintenance of a low surgical mortality and the degree of improvement desired require that the patient be a fair surgical risk, that his lesion be primarily early and predominantly stenotic, and that his myocardium, although strained by overwork, be capable of restoring a normal cardiac output once obstruction of the pulmonary outflow has been relieved. One may then ask: Why operate upon a person who is doing well? Surgery is not indicated, obviously, if a patient is doing well and preliminary and repeated evaluation indicates nonprogression. On the other hand, many patients with established stenosis, although appearing to be reasonably fit, will demonstrate relatively early the progressive nature of their disease. Operative intervention at this earlier date will be repaid by a far better result and a lower mortality rate. Such reasoning may be likened to the urgency surrounding operative intervention in many other diseases, as in tuberculosis or carcinoma, before irreversible and widespread changes have occurred. As in all surgery for chronic progressive disease, what must be done should be done early.

## Anatomic, Pathologic, and Physiologic Considerations

The interplay of anatomic, pathologic, and physiologic factors, with reference to the mitral valve, when reduced to essential components, is readily understandable.

The normal mitral valve may be likened to a truncated cone of thin, flexible membrane. Its base is attached at the left atrioventricular ring, and its apex extends into the left ventricle. The apex and the outer surface of the apical half of this cone are suspended by numerous "guy wires" (chordae tendineae) attached to papillary muscles arising from the ventricular wall near the ventricular apex. The chordae tendineae are grouped more heavily in two areas of the mitral apex, at either side. These areas represent the anatomic fusion of the two components of the valve (an anteromedial and a postolateral leaf), and represent the corners of the apex upon which the leaves fold themselves. The apical portion of the valve cone is somewhat folded or flattened upon these points. When modified by rheumatic disease, these points of folding become the "commissures." The plane of flattening is oblique (with the patient in the supine position), running from the left anterolateral portion of the valve posteromedially. The anterior or anteromedial valve cusp is larger than the posterolateral, and is continuous with the posterior portion of the intracardiac aortic wall. During auricular systole the posterior or posterolateral cusp lies well away from the ventricular wall. During ventricular systole the ventricular wall may approximate and support it. Thus, mitral regurgitation is primarily a defect or dysfunction

of the anteromedial valve cusp. A defect of the posterolateral cusp produces only "limited regurgitation," rather than an uncontrolled reflux of blood, as seen when a defect in the continuity of the anteromedial cusp prevents normal deflection of the ventricular output into the intracardiac aorta. The papillary muscles contract synchronously with the ventricle, drawing the chordae tendineae taut, thus preventing the valve leaflets from becoming inverted or displaced backward into the auricle.

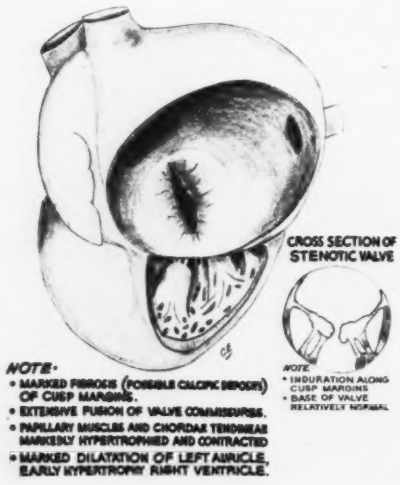


FIG. 1.—Pathologic changes seen in late mitral stenosis. Note the thin, pliable base of the valve (cross section).

In rheumatic disease the mitral valve develops numerous minute cauliflower-like vegetations (1 to 2 mm. in diameter) in a row along the line of closure of the valve. Healing leads to the formation of scar tissue. With repeated infection and healing, there is gradual development of fibrosis, thickening, and narrowing and shortening of the apical portion of the valve cone. This scarring and narrowing may be very limited in extent to resemble merely a purse-string puckering of the valve orifice. In other instances, the disease involves one-fourth to three-fourths of the cone, leaving a flexible margin along its base (fig. 1). In far-advanced disease the whole valve becomes a rigid, completely inflexible, often calcified structure resembling a hard, ovoid placque surrounding a small fish-mouth slit. Most physicians, and even many pathologists, think of such extreme deformity as classical and the rule in mitral stenosis. We have found this condition in only one of our 16 cases.

Usually mitral rheumatic disease hardens or fixes the apex of the mitral cone in the infolded or flattened position so that the commissures become an anatomic reality. Thus stenosis is produced, offering marked resistance to the passage of blood from the left auricle into the left ventricle. Some degree of regurgitation through the mitral slit during ventricular contraction is common. Not infrequently mitral rheumatic disease hardens and shortens the valve cone to a point where the leaves cannot be approximated. Such cases of predominant mitral regurgitation are less common than those predominantly stenotic, and at the present time are not amenable to surgical correction.

Mitral stenosis of any degree interferes with filling of the left ventricle, and thus with the maintenance of normal systemic cardiac output. Many such hearts are unable to increase their output over and above resting bodily requirements. Thus any appreciable amount of work will quickly cause patients with such hearts to become fatigued, dizzy, and even momentarily to lose consciousness. Concurrently, since the egress of blood from the left auricle is impaired, increased pressure within and great dilatation of this chamber results. The high intra-auricular pressure is transmitted to the entire pulmonary vascular system and thence to the right ventricle. A chronic pulmonary hypertension ensues, with nocturnal or exertional pulmonary edema (dyspnea), rupture of pulmonary capillaries (hemoptysis), and failure of the right side of the heart (enlarged liver, ascites, and peripheral edema).

## SURGICAL CONSIDERATIONS

The possible surgical approaches to the problem of mitral stenosis seem to take one of the following three courses: (1) Methods of bypassing the stenotic mitral valve. (2) Methods of relieving the associated pulmonary hypertension. (3) Methods of direct surgical attack upon the stenotic valve.

*By-Passing the Stenotic Mitral Valve.* To our knowledge very little has been attempted or accomplished along the lines of by-passing the mitral valve. In 1913 Jeger[19] suggested that a valved vein might be grafted to serve as an anastomosis between the pulmonary vein and left ventricle, and thereby adequately sidetrack the stenotic mitral valve. Litwak[20] working in our laboratory, has been able to produce such a by-pass by anastomosing a pulmonary vein directly to the left ventricle, utilizing a free graft of azygos, hemiazygos, or femoral vein. This was accomplished in five dogs with function observed for several days, but thrombosis occurred within two weeks to one month in all the dogs.

Satinsky,[21] also in our laboratory, attempted quite a different type of by-pass. He divided the subclavian artery in dogs and anastomosed the distal end of this vessel to a pulmonary vein. The operation was deleterious to normal dogs, causing death, but conceivably might be of some value were the conditions of clinical mitral stenosis present.

*Relieving the Associated Pulmonary Hypertension.* Various methods have been devised to relieve the associated pulmonary hypertension which accompanies mitral stenosis:

1. Harken and his co-workers[15] have suggested that a measure of improvement may be afforded by removal of the cardiac accelerator and afferent nerves to the heart. Relief so obtained is through the production of a slower heart rate, thereby increasing ventricular filling time or by the interruption of pain fibers. He has observed symptomatic relief in a patient so treated, but suggests that such an approach can only be one of palliation. We have had no experience with this form of treatment.

2. Attempts have been made to destroy the function of the tricuspid valve with the production of tricuspid regurgitation to prevent easy access of blood into the right ventricle and lower its pulmonary output.[22] In our opinion such an approach has little to recommend it.

3. The production of a communicating shunt between the pulmonary and systemic venous systems, thus affording a measure of relief to the hypertension within the left auricle, has some merit. An anastomosis between the azygos and pulmonary veins has been accomplished by Sweet[23] with subjective relief of distressing pulmonary symptoms.

4. Both Harken and our group have produced interauricular septal defects to relieve the pulmonary hypertension of mitral stenosis. Such a venous shunt will reduce the hypertension and strain within the left auricle, and secondarily, the associated hypertension throughout the pulmonary vascular bed and right ventricle. We have obtained pressure readings within the pulmonary artery in certain cases of mitral stenosis which were higher than those within the aorta (150+ mm. Hg). Theoretically, a venous shunt should relieve strain on the entire lesser circulation, and one would anticipate relief of such symptoms as hemoptysis, acute attacks of pulmonary edema, and right-sided heart failure. It is probable that such an effect is accomplished to a degree.

Unfortunately, reduction in the left auricular pressure without enlargement of the mitral orifice results in a destruction of the compensatory mechanism which nature has set up to force blood through the narrowed mitral valve. With the production of such a shunt, the left ventricular output falls. The amount of fall is related to the relative sizes of the shunt orifice and the mitral orifice. Obviously, no patient can withstand a shunt if the cardiac output during exercise does not materially increase over the resting requirements. By the same token, it is essential even in those who can so increase their output, that this should not be cut below the level of resting requirements. Since in most clinical cases the patient can do no more than double his resting output, it follows that one should not produce an opening even as large as the stenotic mitral orifice unless it is planned to render the patient totally bed-fast.

It has been repeatedly stated that nature itself has produced a similar combination of defects in the form of Lutembacher's syndrome. Indeed, the syndrome does embrace both a mitral stenosis and a large auricular septal defect. In this instance it must be remembered that compensation has been established over many years by gradual changes in the heart

and by a great increase in the total blood volume. These patients are said to do well, or at least somewhat better than those with "pure" mitral stenosis. Taussig,[23] with reference to this syndrome, states that, "The blood so shunted" (through the auricular septal defect) "passes into the right ventricle and thence is pumped out through the pulmonary artery to the lungs and is again returned by the pulmonary veins to the left auricle. Thus, an excessive amount of blood is pumped around and around the lesser circulation; whereas the left ventricle, aorta, and systemic circulation receive less than their normal quota of blood. The right auricle and ventricle are enlarged. The pulmonary artery is usually twice the size of the aorta. The strain on the left auricle is relieved by the defect in the auricular septum. Therefore, the left auricle is not enlarged. The left ventricle is small." For a time, therefore, the strain on the left auricle and pulmonary vascular bed may be somewhat relieved, but only at the expense of producing a similar strain on the right ventricle, a condition equally serious. Again quoting Taussig, "The late development of cardiac difficulties" (in Lutembacher's syndrome) "occasionally occurs after a relatively minor illness. For example, a patient who has never been known to have any cardiac abnormality, after some *slight* illness may suddenly develop symptoms which lead to progressive heart failure." It would seem that any condition which causes such great pulmonary arterial and right ventricular enlargement can scarcely be considered desirable. Actually, on an average this defect terminates fatally when the subject is 40 years of age: slight, if any, improvement over longevity in uncomplicated mitral stenosis.

Indeed, the production of a venous shunt for mitral stenosis seems somewhat comparable to the production of an arterial shunt (systemic artery to pulmonary artery) for the treatment of congenital pulmonary stenosis. The production of an artificial ductus arteriosus is lifesaving in cases of severe pulmonary stenosis. Too large a shunt is promptly fatal, however, and any arterial shunt increases the load on the myocardium, leading to eventual cardiac enlargement. Helpful as these shunts have been, if a method of direct and successful attack upon the pulmonary stenosis were to become available, we have no doubt that all concerned would promptly embrace the more direct procedure. It would then be necessary, although perhaps not practicable, to recall these patients for the performance of direct valvular surgery and subsequent division of the artificially produced "patent ductus arteriosus." This would also be the case with the venous shunt. If such shunts are created to save life in the face of demonstrably superior direct valvular attack, we will soon be faced with the problem of repairing them.

*Direct Attack Upon the Mitral Valve.* This undoubtedly has been contemplated for many decades. Brunton, in 1902, suggested that the only proper and logical approach to the problem of mitral stenosis was to "lengthen the slit." How sound his judgment was will become evident shortly.

Since the first section of the mitral ring by Elliott Cutler[24] in 1923, there have been a number of direct attacks upon the stenotic mitral valve. The approach and the methods employed have varied. Thus, the left auricular appendage as a site of entrance has been utilized by Allen and Graham (1922),[25, 26] Souttar (1925),[27] the present authors (1945), Smithy (1947), and Harken (1947); the left ventricle by Cutler, Levine, and Beck (1924),[28] Pribram (1925),[29] and Smithy (1947); and the left pulmonary vein by Harken (1946). It is our considered opinion that the approach through the auricular appendage is far superior to any other. It leads directly into the wide opening of the mitral funnel and thence to its stenotic orifice. There are no chordae tendineae to interfere with the passage of the instrument or finger. In addition, no serious disturbance of cardiac rhythm or function is produced. The finger or instrument is well tolerated in the roomy left auricle, unless the actual passage of blood into the ventricle is obstructed for more than three beats. In addition, the appendage may be readily and securely ligated at completion of the operation.

On the other hand, the left ventricular approach is obstructed by chordae tendineae and does not insure ready or accurate localization

of the small opening of the mitral funnel. Such an approach may provoke a serious arrhythmia, does not permit digital insertion or palpation, and may be difficult to close securely.

Methods of dealing surgically with the valve have included: (1) simple incision of a valve cusp, (2) excision of a portion of the mitral ring, (3) digital dilatation of the stenotic orifice, (4) valvuloplasty, and (5) commissurotomy.

1. Simple Incision of a Valve Cusp: Simple incision of a mitral valve cusp has a very deleterious effect upon the experimental animal. If the anteromedial or "aortic" cusp of the mitral valve is completely divided, death is prompt and almost immediate. If the posterior cusp is completely divided, death is usual within twenty-four hours. While Cutler's first patient lived four and one-half years after simple incision, it appears that the cusp was not completely divided. Dogs, too, will tolerate lesser degrees of valve section. One of the objections to simple incision of the ring is the possibility of healing at the site of the incision. It seems improbable that such healing would occur if the valve were widely incised to its base, since the edges would then gape widely during most of the cardiac cycle. On the other hand, if the incision only extended partially through the scar tissue, it could not gape and very probably healing and further cicatrix would occur. We have never observed healing in an adequately incised heart valve in dogs, followed for periods up to twelve months, or in one patient followed three months postoperatively. Of three such patients reported by Cutler, Levine, and Beck, two died shortly after surgery.

2. Excision of a Portion of the Mitral Ring: Simple excision of the valve ring was practiced by Cutler and Levine (1923),[24] by Cutler, Levine and Beck; also by Pribram, and later by Smithy. Since it was felt that the only hope in mitral stenosis was to replace it by a regurgitant type of lesion, partial excision of the valve cusp seemed to be a logical procedure. We are unequivocally opposed to this concept, since experimentally and clinically it has been demonstrated that a suddenly produced mitral regurgitation is poorly tolerated and is as serious a lesion as the original stenosis. Results following this form of treatment have been discouraging in the past. Thus, four patients so treated by Cutler, Levine, and Beck, and one by Pribram, all died within six days after operation. In June, 1948, Smithy reported five living patients out of seven so treated. His better results may be attributed partially to advances in anesthesia and surgery. More pertinent, however, is the fact that by design he excised relatively small pieces of valve tissue. Time will supply the answer as to how well his patients will carry on with their increased, though limited, regurgitation.

3. Digital Dilatation of the Stenotic Orifice: Digital dilatation of the stenotic valve was first practiced by Souttar in 1925 with success in one case. We have since performed three such dilatations with one success.[30, 31] The first of these was attempted on June 12, 1946. In a practically moribund woman a very hard, calcified valve slit was dilated with marked temporary improvement. Death within three days was disclosed at autopsy to have been the result of clotting at the torn commissures. It was evident that the valve had torn at the line of the commissures sufficiently to establish some temporary valve function. Thrombosis had quickly re-established or increased the stenosis and caused death. At postmortem examination the idea of cutting the commissures well into normal valvular tissue under direct digital guidance or "vision" was born. Since that time we have had to resort to simple digital dilation in two additional cases, with one success.[31] We are well aware from studies upon stenotic mitral valves incidentally found at autopsy that simple digital dilatation does not always result in tearing the fused fibrotic commissures. The ring tears at its weakest point, which may well be across a cusp. Even when the tearing does occur at the commissures, one finger is seldom large enough to force the tearing to extend beyond the fibrotic tissue into normal valve structure. However, this early case of dilatation did result in what we then considered to be an entirely new concept of treatment.

4. Valvuloplasty: Harken has used the term "valvuloplasty" to describe his procedure of resection of portions of the valve ring at the commissures. He rightly recognizes that re-

section will best be tolerated if performed at the commissures, assuming that resection with limited or selective regurgitation is the desired result. Two such operations have been performed. In one the pressure in the left auricle was 450 mm. water, but rose above the readings of a 500-mm. manometer after valvuloplasty of this type. This was attributed to a coincident tachycardia. The patient died in pulmonary edema twenty-four hours later. In the other patient, left auricular pressure dropped from 450 mm. water to 400 mm. during the procedure. The patient was improved subjectively. Localization of the commissures was

FIG. 2.—Commissurotomy knife inserted between two gloves on the palmar surface of the right index finger.

accomplished by palpating the valve with the valvulotome inserted through the auricular appendage.

5. Commissurotomy: Commissurotomy is a term suggested to us by Dr. Thomas Durant of Philadelphia to designate the procedure which we have employed to re-establish a marked degree of normal mitral valve function. Our present operative technic is simplified and direct. It has been described in detail in a previous publication. Very briefly, it consists of an operative approach through the left anterior chest wall with the patient in the dorsal recumbent position. The pericardium is incised longitudinally one-half inch anterior to the phrenic nerve as it courses downward over the left lateral aspect of the heart. The huge distended auricular appendage now protrudes from the pericardial sac. A purse-string suture of heavy braided silk is passed about the appendage at its base. A Satinsky clamp is closed over the base of the appendage and a generous portion of its tip is amputated. Two gloves are worn on the right hand. An opening is made in the outer one on the palmar surface at the base of the index finger, and another at the tip. The blade of the commissurotomy knife is inserted between the gloves on the index finger (fig. 2), and the finger is inserted

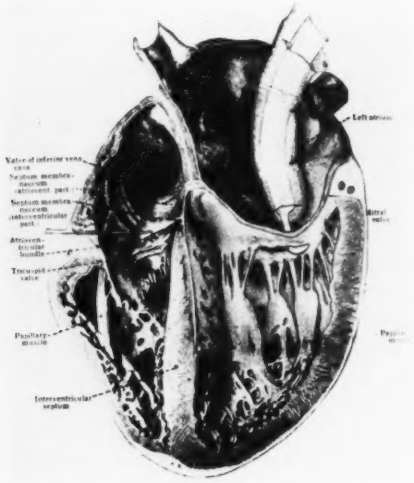

FIG. 3.—Right index finger and commissurotomy knife in left auricle. The stenotic valve is explored; the knife is protruded through the orifice and engaged upon the anterolateral commissure.

into the left auricle as the clamp is released and as the purse-string suture is pulled taut. The finger is well tolerated by the auricle and causes no disturbance to the circulating blood. The valve is quickly and easily located. Its structure can readily be appreciated; the size of the opening and the location of the commissures are determined. The knife is now protruded through the orifice and the hook is engaged upon the anterolateral commissure (fig. 3). A backward stroke usually divides the commissure adequately the first time. The finger again palpates the opening and gently dilates it. If the cut in the commissure does

not extend well into normal tissue the backward stroke is repeated. In patients who have a rather soft valve orifice markedly diminished in cross-sectional area, simple opening of the lateral commissure is in our opinion sufficient. On the other hand, with a rigid, fixed, and sometimes calcified valve, incision of the medial commissure as well may be necessary.

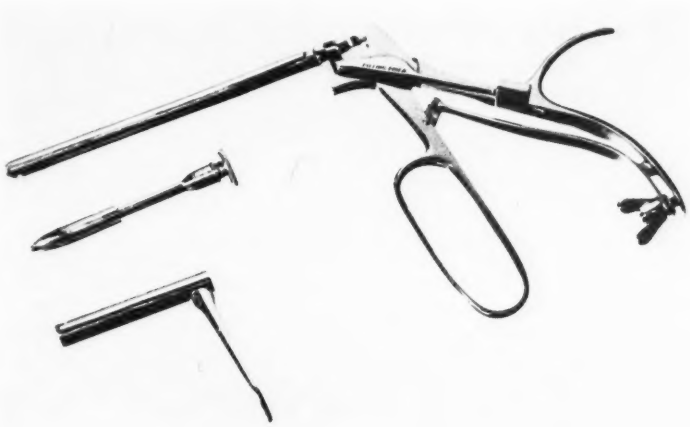

FIG. 4.—Narrow-bladed commissurotomy punch with trocar and cannula

TABLE 1.—*Cardiac Catherization Studies in One Patient* (J. B., Case 6)

| Pressure in mm. Hg | Preoperative (1/21/49) | | | | | Postoperative (3/3/49) | | | | | Immediately Before Commissurotomy (2/2/49) | | | Immediately After Commissurotomy (2/2/49) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Systolic | | Diastolic | | Pulse | Systolic | | Diastolic | | Pulse | Systolic | Diastolic | Pulse | Systolic | Diastolic | Pulse |
| | Max. | Min. | Max. | Min. | | Max. | Min. | Max. | Min. | | | | | | | |
| Right pulmonary artery | | | | | | 48.5 | 40.8 | 16.1 | | 80 | | | | | | |
| Main pulmonary artery | | | | | | 51.2 | 48.4 | 16.1 | | 80 | | | | | | |
| Right ventricle | 96.2 | 83.2 | 19.6 | 14.0 | 85 | 48.6 | 39.7 | 2.7 | −2.7 | 72 | | | | | | |
| Right auricle | 17.4 | 9.38 | 4.55 | 1.4 | 83 | 9.9 | 6.4 | 3.4 | 0.7 | ? | | | | | | |
| Left auricle | | | | | | | | | | | 45.1 | 30.3 | 90 | 15.5 | 2.6 | 96 |

This is accomplished by pronating the hand, engaging the medial commissure, and repeating the cutting maneuver as described above.

In order to handle very hard or calcified valves, we have prepared a special narrow-bladed backward-cutting punch (fig. 4). This has a long bite so that it, too, will cut completely through the diseased tissue and into the flexible membranous valve. Thus, we still obtain practically the same effect as by simple incision of the commissures but without the advantage of simultaneous digital guidance.

The finger and knife are now deftly withdrawn from the auricle as the previously placed purse-string suture is drawn tight, preventing more than a few cubic centimeters of blood loss The suture is tied and the cut edge of the appendage is oversewn. There should be no disturbance of the systemic circulation and few if any irregularities throughout the procedure.

Postoperatively the patient may experience considerable pain for three to four days from the manipulative "pericarditis." This is controlled by opiates. Ambulation is permitted within two to five days.

It is our present belief that commissurotomy by such a technic is a simple, relatively safe, direct method of re-establishing improved valve

function. It has the great advantage of direct digital guidance. It should not, and has not in any of our five successful cases, produced any detectable amount of mitral regurgitation. Blood loss is minimal and no apparent disturbance of heart function results. That it effectively accomplishes the desired result is shown not only by the marked clinical improvement in all living patients, but also by objective physiologic studies.

The following representative table (table 1) reveals the pressure changes observed in one of our patients studied before and after commissurotomy. All pressures were recorded with a Lilly electronic manometer. The pressures in the left auricle were taken directly with the heart exposed immediately before and immediately after cutting the valve. Two other patients studied in this manner showed similar changes which have been published elsewhere.[31] In none of these patients was there any appreciable blood loss, significant change of rate or rhythm, or disturbance of systemic circulation. We believe that these changes in the left auricular pressure indicate two things: first, the mitral stenosis was at least partially relieved or pressure would not have fallen; second, no appreciable increase in pre-existing regurgitation was produced or the pressure would have risen.

Long-term follow-up alone can supply the ultimate answer to the effectiveness of commissurotomy. Nevertheless, since years must elapse for such information to become available, we feel justified in proceeding in those patients who meet our present rigid indications and in whom it might be lifesaving. In this our thinking follows the line already established by Blalock and Taussig in their work on pulmonary stenosis. The day will undoubtedly come when an extracorporeal circulation will permit exclusion of the heart and lungs from active duty during intracardiac surgery. At that time it will be possible to open the heart widely and perform plastic procedures upon the valves and septa under direct vision. Such operations as commissurotomy will then become antiquated.

## Results of Commissurotomy

Our early results were discouraging, but with improved selection of cases they have begun to show promise. A summary of our experience with commissurotomy to date is appended in table 2. An abstract of each case has appeared in a previous publication.[31]

Table 2.—*Mitral Stenosis*

| Patient | Date of Operation | Type of Operation | Result |
|---|---|---|---|
| 1. W. W. | 3/22/48 | Commissurotomy | Death in 6 days; technical difficulty |
| 2. C. W. | 6/10/48 | Commissurotomy | Living; excellent result |
| 3. S. S. | 6/27/48 | Commissurotomy | Living; excellent result |
| 4. F. G. | 7/13/48 | Commissurotomy | Death in 8 days; sudden cerebral embolus |
| 5. A. W. | 9/ 2/48 | Commissurotomy | Death in 24 hours; hemorrhage |
| 6. J. B. | 2/ 2/49 | Commissurotomy | Living; excellent result |
| 7. S. C. | 3/23/49 | Commissurotomy | Living; excellent result |
| 8. E. W. | 4/20/49 | Commissurotomy and dilatation | Living; improved |

Commissurotomy by the technic described was performed in 8 cases with three fatalities. In the first of these (Case 1) a modified scalpel was employed, as our present commissurotomy knife had not been perfected. Attempts to incise the commissures were attended by repeated disengagement of the blade as it rode over the fibrotic valve, resulting in an inadequate incision extending only a few millimeters into the scar tissue. Pre- and postoperative pressure determinations in the left auricle were unchanged (320 mm. of water). The patient died on the sixth postoperative day in pulmonary edema from unrelieved mitral stenosis. The second patient (Case 4) was operated upon accurately and well, and appeared to be well

on the way to a most satisfactory result, but suffered a cerebral embolus and died suddenly on the seventh postoperative day. Autopsy disclosed an adequate and satisfactory commissurotomy. Thrombus formation had occurred in the left auricular appendage, from which the embolus apparently originated. We had observed such thrombus formation many times in animal appendages after valve surgery, but no adverse complications resulted. We had simply oversewn the incision in the appendage at the conclusion of the procedure. In the

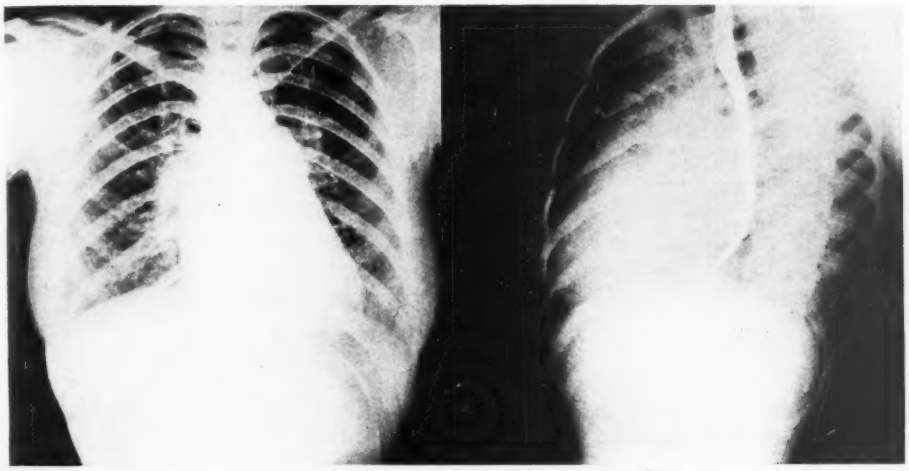

FIG. 5.—Anteroposterior and right anterior oblique preoperative roentgenograms showing size of heart and left auricle (Case 1).

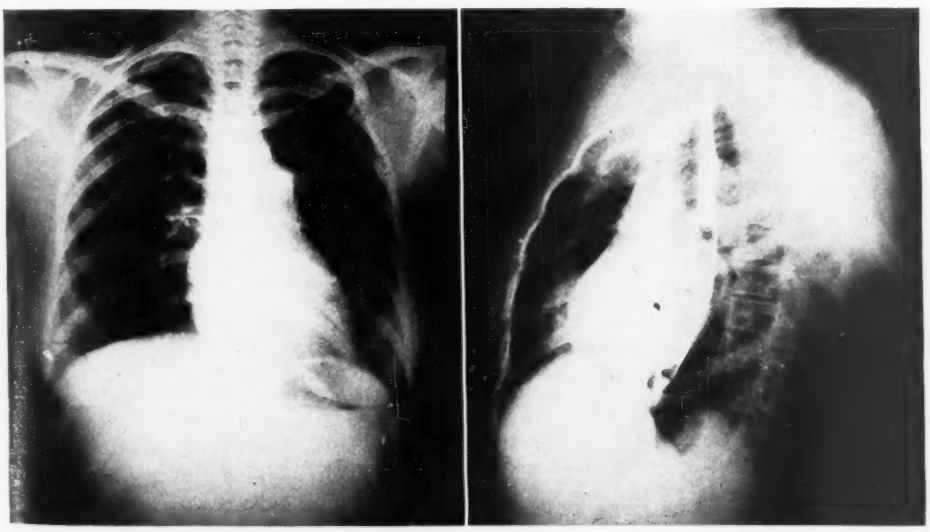

FIG. 6.—Anteroposterior and right anterior oblique roentgenograms made six months postoperatively showing reduced size of heart and left auricle and disappearance of pulmonary vascular congestion (Case 1).

4 succeeding cases (and in one previous one C. W., without purposeful design) we have ligated the auricular appendage at its base to prevent such disaster. The appendage of the third patient operated upon shortly thereafter was ligated at its base without suture of the cut tip. Autopsy indicated that hemorrhage had occurred from this site (Case 5). This experience has led to both ligation at the base and an oversewing suture at the cut tip on all subsequent cases.

The remaining 5 patients represent most satisfactory results. Four patients are clinically well. Two who had been digitalized for some months prior to surgery no longer need such medication. There is definite diminution in the size of the heart as shown roentgenographically (figs. 5 and 6). Their tolerance for exercise is remarkably increased, permitting them to return to normal activity. Careful examination reveals some slight residual evidence of mitral stenosis in 2 of the patients (Cases 2 and 6) and somewhat more in a third (Case 8) in whom conditions were not satisfactory for an ideal commissurotomy. The others have no residual signs of the disease, although admittedly the follow-ups are of short term. Electrocardiographic follow-up shows no significant change from the preoperative state. There has been no evidence of increased mitral regurgitation in any of the 5 patients.

## Indications and Contraindications for Surgery (at Present)

The indications and contraindications for commissurotomy must be considered together. Both must change as experience dictates. Common sense and our present experience have led to certain conclusions to date:

1. *Most favorable group:*
   - A. Excessive fatigability.
     Increasing exertional dyspnea.
   - B. No rheumatic activity.
     Normal sinus rhythm.
     Lesion predominantly stenosis.
     Evidence of significantly increased pulmonary hypertension.
2. *Less favorable group:* The above plus:
   - A. Recurrent bouts of hemoptysis.
   - B. Arterial embolic phenomena.
   - C. Auricular fibrillation without failure.

Hemoptysis in more than amounts necessary to stain the sputum is of grave import. Wolf and Levine[32] point out that in their series of cases the average duration of life following the onset of severe hemoptysis is 35.5 months. Levine[33] stated that the average duration of life following the initial attack of congestive failure is 4.6 years. The development of auricular fibrillation is usually permanent and irreversible. In this state thrombus formation not infrequently occurs along the endocardium of the dilated and relatively immobile auricular walls. Some 75 per cent of these occur within the lumen of the auricular appendage (left), a common site for the origin of arterial embolization.

It follows, then, that our contraindications would be: (1) Active rheumatic infection. (2) Presence of superimposed subacute bacterial endocarditis. (3) Cardiac failure uncontrollable by medical means. (4) Presence of marked associated mitral regurgitation or other valve (aortic) deformities.

## Summary

Our entire experience with commissurotomy for mitral stenosis (8 cases) has been reviewed. There have been four very satisfactory results, one fair result, and three deaths. Had our present knowledge been applied to all cases, the mortality might have been appreciably lower.

Commissurotomy is a simple, direct, effective, and safe procedure. Its exact surgical technic has been outlined.

Commissurotomy accomplishes relief of mitral stenosis by restoring considerable valve function without the production of additional mitral regurgitation.

Digital guidance in the performance of accurate valve surgery is essential until a method of direct vision becomes established.

The left auricular appendage is the most satisfactory avenue of approach to the mitral valve.

The auricular appendage must be ligated at the conclusion of the procedure to prevent arterial embolization. This may prove to be the proper approach to the management of arterial embolization in many cases of auricular fibrillation unassociated with mitral stenosis.

An appreciably enlarged left ventricle in a case of supposed "pure mitral stenosis" is indicative of some additional significant valve lesion (aortic stenosis or regurgitation, or mitral regurgitation) and is by our present criteria contraindicative to commissurotomy.

Study methods of value in addition to clinical evaluation embrace cardiac catheterization for determination of pulmonary vascular pressure, ballistocardiography, and other physiologic studies for the determination of cardiac output.

Venous shunts for the treatment of mitral stenosis are of some value, although their eventual effects upon cardiac output, the right ventricle, and the lesser circulation must be kept clearly in mind.

### Addendum

Twenty-two additional cases of advanced mitral stenosis have undergone commissurotomy since this paper was submitted for publication, bringing the total series to 30 Six patients died. In 21 the results have been satisfactory to date, both subjectively and by objective improvement similar to that noted in table 1. In 3, improvement has been considerable subjectively, but less striking objectively.

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# Experimental Hypervolemic Heart Failure: Its Bearing on Certain General Principles of Heart Failure

*By* William Huckabee, M.D., Gus Casten, M.D., and T. R. Harrison, M.D.

Infusion of large volumes of fluid into normal dogs produces a progressive rise in venous pressure with an initial parallel rise in cardiac output succeeded by a fall. On the basis of these experiments and other considerations which are discussed, it is concluded that the cardinal hemodynamic defect common to all types of heart failure is a disproportion between inflow load and cardiac output. The various general circulatory disorders are classified as primary disorders of filling and primary disorders of emptying with various subgroups.

THE PURPOSES of the present communication are threefold: (1) to present experimental data concerning a type of heart failure to which relatively little attention has been paid in the past; (2) to consider the similarities between heart failure produced experimentally and that occurring in patients; (3) to offer a classification of heart failure which appears to be applicable to both conditions.

In the heart-lung preparation, failure may be induced by (1) gradual exhaustion of the myocardium, (2) excessive increase in the peripheral resistance, (3) excessive elevation of the venous reservoir. The first factor is the most important because it occurs spontaneously with the passage of time, and because the myocardial competence determines at all times the degree of load (arterial or venous) which is required to produce failure.

When we turn from the heart-lung preparation to the patient, it becomes clear that the first (myocardial exhaustion) and second (excessive arterial resistance) mechanisms of heart failure have well-recognized clinical analogues.* It is in regard to the third type of heart failure (that analogous to elevation of the venous reservoir) that uncertainty exists.

It has long been recognized that, whereas heart failure in man is usually associated with decline in the cardiac output per unit of time, in some cases this function may be normal or increased. This conclusion, originally based on older studies, with less accurate methods,[1, 2] has now been amply confirmed by newer studies with more accurate methods.[3, 4] In recent years the term "high-output failure"[5] has been applied to patients with this functional disturbance. The present communication represents an attempt to analyze the mechanisms of "high-output failure," and to relate them to the mechanisms of heart failure in general.

Before proceeding further with the general consideration of the principles of heart failure, it will be well to consider certain experiments which may possibly be of aid in the clarification of these principles. In these experiments as in those of previous investigators[6–8] heart failure was induced by massive intravenous infusions.

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* The classic analogue of heart failure developing spontaneously over a period of hours in the heart-lung preparation is that developing over a period of decades in man, i.e., senile heart failure occurring in the absence of demonstrable increase in load. The common causes, in patients, of heart failure analogous to that brought about by excessive increase of the artificial resistance in the heart-lung preparation, are hypertension and aortic stenosis. However, the analogy is relative rather than absolute, because heart failure due to these causes is rare in young subjects, and in older subjects one can never be certain concerning the relative importance of the resistance factor as compared to the myocardial aging factor. A rarer but better analogy is heart failure occurring acutely in young subjects with previously normal hearts as the results of multiple pulmonary embolism.

TABLE 1.—*Effect of Rapid Intravenous Infusions on Cardiac Output and Related Functions*

| Experiment | Sample No.* | Cardiac Output | Increase of Rt. Atrial Pressure Over Control Value | Veno-Atrial Pressure Difference | Arterio-venous $O_2$ Difference | Mean Arterial Blood Pressure | Volumes Infused |
|---|---|---|---|---|---|---|---|
| | | *L/min.* | *cm. saline* | *cm. saline* | *vol. %* | *mm. Hg* | |
| 1. 5% albumin in water, 4.4 cc./Kg./min. | 1 | 1.46 | 0 | 2.8 | 2.64 | 60 | 1700 cc. in 27 min. |
| | 2 | 2.29 | 18.5 | 5.0 | 1.95 | 56 | |
| | 3 | 1.57 | 39.0 | 1.5 | 3.27 | 94 | |
| | 4 | 2.55 | 12.0 | 1.5 | 2.01 | 94 | |
| | 5 | 2.98 | 4.5 | | 1.87 | 94 | |
| 2. 5% albumin in water 3.3 cc./Kg./min. | 1 | 2.23 | 0 | 2.0 | 3.90 | 92 | 2173 cc. in 53 min. |
| | 2 | 6.08 | 2.2 | 3.3 | 1.75 | 124 | |
| | 3 | 2.98 | 26.7 | 1.8 | 2.91 | 128 | |
| | 4 | 2.55 | 29.2 | 2.0 | 3.12 | 114 | |
| 3. 5% albumin in water 3.3 cc./Kg./min. | 1 | 1.30 | 0 | 4.0 | 7.08 | 140 | 2810 cc. in 52 min. |
| | 2 | 2.75 | 5.0 | 5.5 | 5.48 | 170 | |
| | 3 | 7.48 | 8.0 | 10.0 | 3.06 | 174 | |
| | 4 | 3.92 | 10.5 | 5.0 | 4.76 | 190 | |
| | 5 | 4.40 | 7.0 | 11.0 | 4.69 | 150 | |
| 4. 5% albumin in water, 3.3 cc./Kg./min. | 1 | 3.50 | 0 | 5.0 | 2.23 | 114 | 1355 cc. in 25 min. |
| | 2 | 6.35 | 8.0 | 2.0 | 1.59 | 150 | |
| | 3 | 4.02 | 15.0 | 1.5 | 4.21 | 146 | |
| | 4 | 3.26 | 31.0 | 3.0 | 4.84 | 134 | |
| | 5 | 2.84 | 32.3 | 1.3 | 4.58 | 100 | |
| | 6 | 1.99 | 11.5 | 0.3 | 3.57 | 136 | |
| 5. 5% albumin in modified Ringer's solution, 33 cc./Kg./min. | 1 | 3.67 | 0 | 6.3 | 2.53 | 98 | 2590 cc. in 68 min. |
| | 2 | 3.74 | 4.5 | 5.3 | 3.04 | 108 | |
| | 3 | 3.87 | 9.8 | 3.5 | 3.08 | 110 | |
| | 4 | 4.43 | 15.8 | 1.5 | 2.57 | 96 | |
| | 5 | 4.28 | 18.3 | −3.5 | 2.19 | 96 | |
| | 6 | 1.56 | 23.3 | −6.5 | 1.56 | 80 | |
| 6. 10% albumin in modified Ringer's solution, 3.3 cc./Kg./min. | 1 | 5.71 | 0 | 4.3 | 1.98 | 110 | 1435 cc. in 26 min. |
| | 2 | 9.59 | 8.3 | 4.5 | 1.47 | 120 | |
| | 3 | 6.00 | 12.8 | 0.5 | 2.31 | 134 | |
| | 4 | 5.82 | 18.8 | 1.8 | 2.27 | 134 | |
| | 5 | 5.20 | 25.3 | 1.0 | 2.46 | 132 | |
| | 6 | 3.59 | 15.3 | 4.5 | 4.01 | 148 | |
| | 7 | 2.01 | −1.8 | 17.8 | 6.25 | 116 | |
| 7. 10% albumin in water, 3.3 cc./Kg./min. | 1 | 1.81 | 0 | .8 | 6.03 | 134 | 1095 cc. in 21 min. |
| | 2 | 11.30 | 4.8 | 1.3 | 0.99 | 160 | |
| | 3 | 8.92 | 9.0 | | 1.70 | 164 | |
| | 4 | 4.37 | 15.0 | | 2.93 | 160 | |
| | 5 | 3.57 | 23.5 | | 4.75 | 166 | |
| | 6 | 2.85 | 1.5 | | 4.97 | 120 | |

TABLE 1.—*Concluded*

| Experiment | Sample No.* | Cardiac Output | Increase of Rt. Atrial Pressure Over Control Value | Veno-Atrial Pressure Difference | Arterio-venous $O_2$ Difference | Mean Arterial Blood Pressure | Volumes Infused |
|---|---|---|---|---|---|---|---|
| | | *L/min.* | *cm. saline* | *cm. saline* | *vol. %* | *mm. Hg* | |
| 8. Heparinized horse blood, 3.08 cc./Kg./min. | 1 | 1.10 | 0 | 14.3 | 8.3 | 100 | 2865 cc. in 73 min. |
| | 2 | 3.37 | 8.3 | 12.0 | 3.03 | 110 | |
| | 3 | 3.23 | 21.3 | | 3.15 | 136 | |
| | 4 | 2.65 | 30.3 | | 3.49 | 150 | |
| | 5 | 1.13 | −0.5 | | 7.18 | 100 | |
| 9. Heparinized dog blood, 3.3 cc./Kg./min. | 1 | .34 | 0 | 6.5 | 10.24 | 92 | 3500 cc. |
| | 2 | .78 | 5.0 | 3.5 | 5.83 | 120 | |
| | 3 | 1.07 | 8.5 | 0.5 | 5.58 | 134 | |
| | 4 | 1.24 | 17.8 | −0.8 | 4.07 | 154 | |
| | 5 | 1.10 | 11.8 | −1.0 | 6.30 | 136 | |
| | 6 | .85 | 22.0 | 1.3 | 5.52 | 144 | |
| | 7 | .77 | 31.3 | 0.8 | 5.55 | 128 | |
| | 8 | .57 | 1.5 | 3.3 | 8.63 | 106 | |
| 10. 15% albumin in modified Ringer's solution variable rate | 1 | 1.19 | 0 | 7.5 | 7.10 | | 2730 cc. in 183 min. |
| | 2 | 3.05 | 10.3 | 1.8 | 3.48 | | |
| | 3 | 4.84 | 10.8 | 1.0 | 2.15 | | |
| | 4 | 4.33 | 12.8 | 0.5 | 1.94 | | |
| | 5 | 3.26 | 16.3 | 0.0 | 1.73 | | |

* In each experiment the first sample represents the control values. Values below the cross line represent measurements made after cessation of the infusion, while the intermediate observations were made during the infusion.

## EXPERIMENTAL FINDINGS

Hypervolemia was produced in morphinized dogs by intravenous infusion of various fluids, including blood, serum albumin solutions, and modified Ringer's solution. Cardiac outputs were determined according to the Fick principle, using the blood oxygen technic of Van Slyke and Neill and the Benedict apparatus for recording oxygen consumption. Venous samples were obtained from the right atrium by a cannula passed down from the external jugular vein. Arterial, venous, and atrial pressures were measured directly by means of mercury and saline manometers.

Autopsies revealed pulmonary and hepatic congestion, pulmonary edema, and cardiac dilatation.

The more pertinent experimental findings are presented in table 1. Pulse rates changed relatively little so that, in general, stroke volume paralleled minute output. (The relative constancy of the pulse rate in these experiments was probably due to the narcotic for morphine is a strong vagal stimulant in the doses used.) Slight to moderate rise in arterial pressure occurred. The arterial oxygen saturation exhibited variable changes, being sometimes low during the control observations (apparently consequent to morphine narcosis) and at another times declining during the experiment (pulmonary edema). In several instances the arterial oxygen saturation remained above 95 per cent throughout the experiment. The arterial oxygen content declined rapidly when albumin solutions were employed but remained essentially unchanged when blood was used for infusion. The arteriovenous oxygen difference characteristically decreased after the start of infusion and increased again at the time of the fall in cardiac output; it usually did not become greater than the control value. Thus even after the onset of heart failure the cardiac output tended to be elevated in proportion to the oxygen consumption.

*Venoatrial Pressure Difference.* During the control periods the femoral venous pressure usually exceeded the right atrial pressure by 2 to 7 cm. of water. When the infusion was begun, both pressures increased steadily and the pressure difference at first exhibited variable changes. Prior to the beginning of the decline in cardiac output the atrial pressure rose more rapidly and the two pressures approached each other. It should be emphasized that marked elevation of cardiac output was frequently encountered at a time when the venoatrial pressure difference was sharply reduced.

*Cardiac Output and Atrial Pressure.* During the control period the atrial pressures, cardiac outputs, and arteriovenous oxygen differences exhibited wide variations in different dogs. However, the effects of the infusion were qualitatively similar in all of the animals. Several typical experiments are shown in figure 1. The atrial pressures and cardiac output values for all of the experiments are plotted in figure 2.

With the progress of infusion, the atrial and peripheral venous pressures increased steadily. Accompanying the increased filling pressure was an initial rise of cardiac output. As the

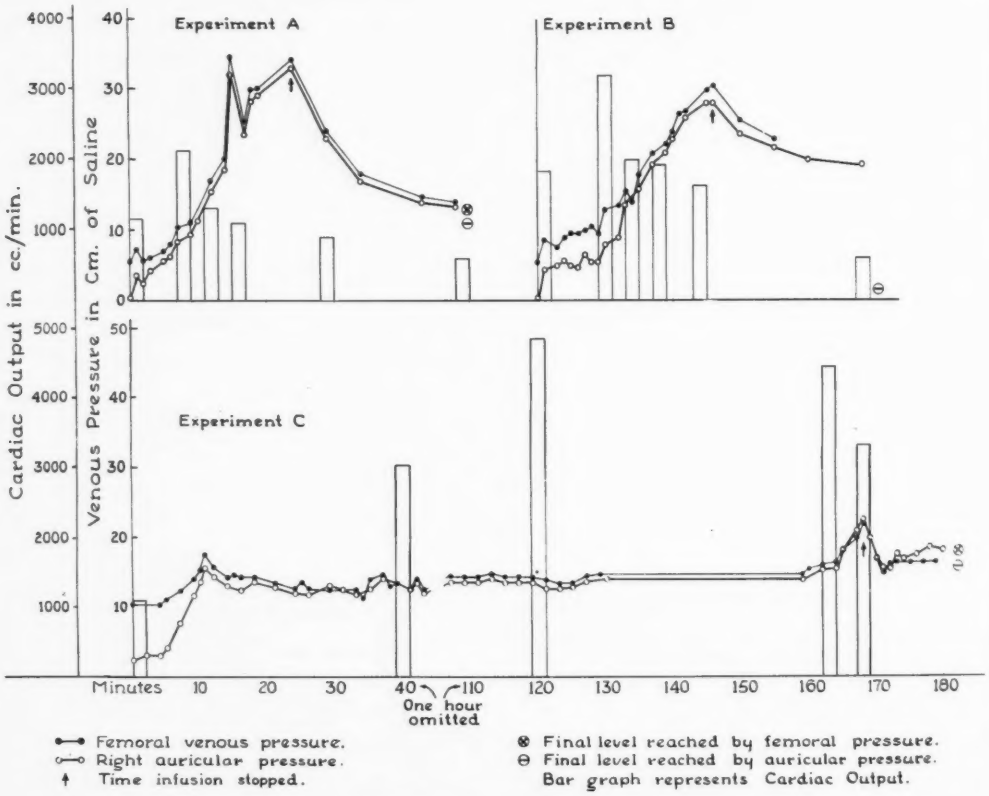


FIG. 1.—Variation of venous and atrial pressures and cardiac output during infusion. *A*, Infused with 5 per cent albumin in distilled water, 3.3 cc. per Kg. per minute. The break in the curve has not been accounted for; bleeding may have occurred internally. *B*, Infused with 10 per cent albumin in modified Ringer's solution 3.3 cc. per Kg. per minute. *C*, Infused with 15 per cent albumin in modified Ringer's solution at a variable rate to keep atrial pressure constant, a total of 2,730 cubic centimeters. Note that the femoro-atrial venous pressure difference always decreased while the cardiac output was still increasing. Such a relationship could only result from an increasing size of the venous stream bed (see text).

infusion continued the venous pressure continued to increase, but the cardiac output began to rise less rapidly, and finally declined.

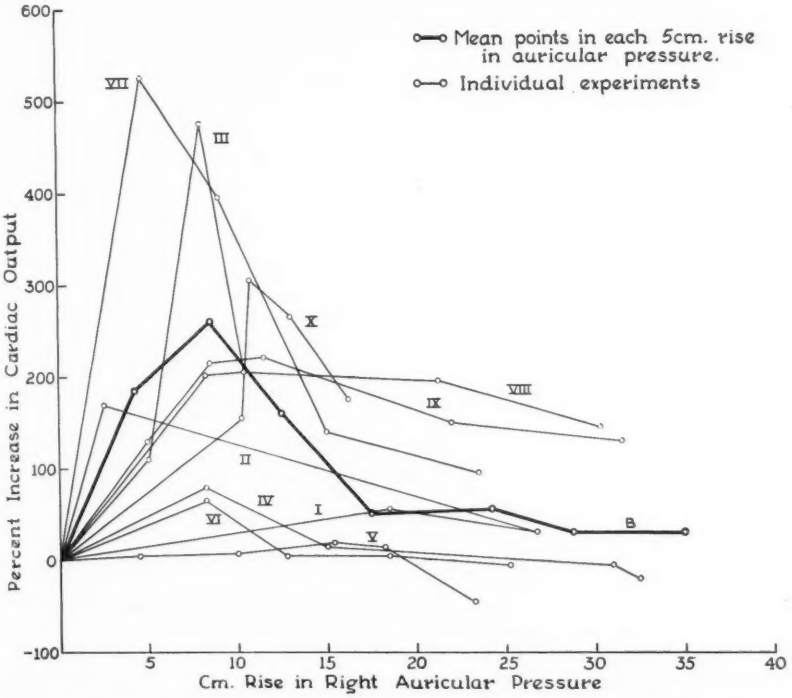


FIG. 2.—Variation of cardiac output with right atrial pressure. All the experiments are represented as graphs in which cardiac output is plotted against right atrial pressure during the time infusion was in progress. The points on the mean curve "B" are located on the mean ordinate and mean abscissa of all the points in each 5-cm. rise of atrial pressure. It should be noted that the first portion of this curve has the same shape as the classical Starling curve for the heart-lung preparation. The failure of the latter portion of this curve to continue to decline is thought to be due to the protective effect of the pericardium.

If, at this point, the infusion was stopped, the atrial pressure usually underwent a slight further increment for a minute or two and then slowly declined during the next hour. Stopping the infusion resulted in variable directional alterations in cardiac output.

In one instance (table 1, Exp. 10) the atrial pressure was maintained at a constant and somewhat elevated level by varying the rate of infusion. Later a spontaneous rise in pressure occurred and this persisted after the infusion was stopped.

The mean curve of cardiac output in relation to atrial pressure (fig. 2) is similar to the curve found for the heart-lung preparation by Starling.[9] The plateau of this curve at the end in the intact animal was not found by Starling and may represent the effect of the pericardium in preventing further dilatation of the heart.

## DISCUSSION

### *Interpretation of Experimental Observations*

The experiments which have been presented were highly artificial. Huge amounts of infusate were required to produce heart failure. The different animals exhibited marked variation in quantitative relationships between venous pressure and cardiac output. Nevertheless, the qualitative responses were similar in all of the animals and were not different in the experiments characterized by anemic anoxia and elec-

trolyte dilution (owing to the administration of serum albumin solution) from the more physiological experiments (in which blood was administered). Two findings were constant. (1) As the infusion progressed and the venous pressure rose steadily the cardiac output first increased and then decreased. (2) The difference between the peripheral venous and right atrial pressures at first increased or remained constant and them diminished even though the cardiac output was still rising. Since this observation appears somewhat paradoxic, its significance may now be considered.

The quantitative aspects of the conditions determining the flow of a liquid through a set of rigid capillary tubes (Poiseuille's law) are expressed by the formula $Q = \frac{(P_1 - P_2)\pi r^4}{8\mu l}$, in which $Q$ is the volume flow, $P_1$ and $P_2$ are the pressures at the two ends of the tube, $r$ is the radius, $l$ the length, and $\mu$ the coefficient of viscosity. In the body the two latter functions tend to be constant and since the blood vessels are not rigid, the formula does not apply quantitatively even to flow in the large vessels. For purposes of simplification a rough expression of the conditions existing in the veins may be achieved by combining the constants ($8$, $\pi$, $\mu$, and $l$) and substituting for $r^4$ a value ($R$) related to the radius but not necessarily a fixed exponent thereof. The formula then becomes $Q = K(P_1 - P_2)R = KRP_1 - KRP_2$. It is apparent that the flow of blood into the atrium from the veins will depend on the difference in pressure and on the radius of the veins. If the latter factor remains constant, the atrial inflow will be increased by a rise in peripheral venous pressure and will be diminished by a rise in atrial pressure. If the pressures remain constant, the flow will be markedly affected by alterations in the cross-sectional diameter of the veins. The increase in size of the vascular system accounts for the difference in the cardiac output of an infant and an adult with the same venous and atrial pressures. When the filling of the atria and ventricles from the venous system is considered, it is apparent that Poiseuille's law is not applicable because one is no longer dealing with flow through rigid tubes but with flow into expansile chambers. However, the principle that certain factors (corresponding to $KRP_1$) tend to increase filling and others (corresponding to $KRP_2$) tend to decrease it is still valid.

The failure to find a strict parallelism between venous pressure and cardiac output has been noted by others in studies on man and has led some to question the validity of the Starling concept of the relation between the filling and the output of the heart. However, certain differences between the heart-lung preparation and the intact animal should be considered.

In the heart-lung preparation the pulse rate and the peripheral resistance are artificially fixed, while in the intact animal these functions are variable. Thus the adjustment of cardiac output to muscular exercise appears to be accomplished not only by increase in heart rate but also by decline in peripheral resistance.[10] The latter adjustment makes it possible for the heart to empty more completely during systole and hence to expel a greater volume per beat without increase in diastolic size or energy expended.[11] The decline in the volume of blood in the ventricle at the onset of diastole will result in reduction of the ventricular diastolic pressure ($P_2$ in Poiseuille's formula) and hence will cause increased filling if other factors remain constant.

In the heart-lung preparation the venous reservoir is connected to the heart by relatively inflexible rubber tubing and hence the inflow into the heart will tend to vary directly with the height of the venous reservoir. In the intact animal the veins are readily distensible and any change in their radius ($r$ in Poiseuille's formula) will be reflected by a marked difference in filling if other factors remain constant.

These considerations make it clear that the conditions affecting diastolic inflow (and hence systolic output) are more complex in the intact animal than in the heart-lung preparation. The tendency to fill, i.e., the amount of blood "offered" the heart from the venous system, depends, in the intact animal, not only on the venous pressure but also on the cross-sectional diameter of the veins. However, the actual filling will depend, not only on these factors, but also on the pressure existing within the cardiac chambers during filling, i.e., on the atrial and ventricular diastolic pressures. Because of the large size of the atrioventricular orifices these pressures may be considered as being essentially identical.

The dynamics of ventricular filling may be simplified by grouping together the factors which tend to increase and decrease this func-

tion, respectively. One may therefore use the term "inflow load" ($KRP_1$ above) to designate the tendency of the venticle to fill or the amount of blood offered the ventricle.* *The inflow load may be defined as the amount of blood which would enter the ventricle during diastole if the ventricular diastolic pressure remained at zero throughout diastole.* However, the ventricular diastolic pressure does not so behave. At the onset of diastole its level depends on the amount of residual blood, i.e., on the completeness of emptying of the previous systole. As blood enters the ventricle during diastole the pressure rises. Any increment of ventricular diastolic pressure causes impairment of filling (corresponding roughly to $KRP^2$ above) and hence is immediately reflected in a rise in atrial pressure. The actual filling of the ventricle therefore varies directly with the inflow load and inversely with the ventricular diastolic pressure. As a rough and qualitative approximation of conditions in the body, Poiseuille's formula may be modified and written as follows: Ventricular Filling $\propto$ Inflow Load—Ventricular Diastolic Pressure.

When the original Starling curve[9] and the rather similar curve as obtained in these experiments (fig. 2) are examined in relation to these concepts, certain points emerge. (1) In the heart-lung preparation it is justifiable to consider venous pressure as a direct index to inflow load because the rubber tubing connecting the venous reservoir is relatively rigid. (2) In the intact animal the veins are readily distensible and an initial slight rise in venous pressure will tend to cause increase in their diameter, while at high levels of venous pressure the veins are already fully distended and further slight increment of pressure will cause little or no increase in venous diameter. Hence a linear relationship between inflow load and venous pressure does not exist in the intact animal. If other factors remain constant, minimal rise from the normally low level of venous pressure will tend to be reflected in large increments in cardiac output (table 1, fig. 2) but at high levels of venous pressure further increment will have little effect (fig. 2). (3) The plateau at the terminal portion of the curve in figure 2 is not found in the heart-lung preparation and is presumably due to the intactness of the pericardium.

In the experiments reported in this study the heart at first responded to the increase in inflow load produced by the infusion by a well-marked increment in output. As the load was further increased the response became less marked and eventually the heart failed to respond further but actually pumped less blood than before. Since, over any significant period of time, the inflow and the output are necessarily the same, it is clear that the decline of output of the ventricles was necessarily associated with decline of inflow. It is clear from the preceding discussion that such a decline of inflow in the presence of a steadily rising inflow load must have been induced by an increasing hindrance to filling, i.e., by a rise in the ventricular diastolic pressure. This in turn could have been only due to diminished completeness of systolic emptying and it is noteworthy that this occurred at a time when the actual cardiac output was markedly elevated.

The sequence of events as portrayed in figure 2 was evidently as follows. During the initial phase of the infusion the infusate was evidently relatively evenly distributed throughout the venous system, the diastolic volume of the ventricle increased sharply with relatively little increase in systolic volume. (In fact it would appear that the systolic volume and the initial ventricular diastolic pressure may have diminished in those experiments in which the peripheral venous pressure rose more rapidly than the auricular pressure.) At a later stage of the infusion the systolic volume evidently increased at about the same rate as the diastolic volume and the cardiac output tended to remain relatively constant despite the rising venous pressure. At this time the rise in ventricular diastolic pressure was reflected in a sharp rise in atrial pressure so that the femoral-atrial pressure difference decreased

* The term "venous load" is simpler and might seem preferable but has one important defect. Aortic and pulmonic insufficiency are states which tend to increase the inflow load without necessarily increasing the venous load. The term "inflow load" will therefore be employed in the discussion to follow.

sharply. Under such circumstances the high level of output could have been sustained only by a large inflow consequent to an outspoken increase in the diameter of the venous system. At a later stage of the experiments the absolute decline in cardiac output, despite the additional increment in filling pressure, could have been due only to an additional rise in ventricular diastolic pressure associated with a further sharp increase in systolic volume with a lesser or no increase in diastolic volume.

*The hemodynamic defect responsible for heart failure in these experiments* is therefore clear. Heart failure occurred when cardiac output failed to keep pace with inflow load and this discrepancy was brought about by decline in filling consequent to increase in ventricular diastolic pressure. The increase in ventricular diastolic pressure was evidently due to passive cardiac dilatation as the result of incomplete systolic emptying, even though the actual systolic output was much greater than normal. The experiments illustrate that the degree of systolic emptying and the systolic output may vary in opposite directions.

Although the venous pressure rose steadily while the infusion was maintained, differences occurred in the rate of rise in different parts of the venous system. Initially the increment in the femoral vein was the same as or slightly greater than that in the right atrium. Soon, however, the pressure began to rise more rapidly in the atrium than in the periphery. Since it is generally agreed that heart muscle lacks tone (in the sense of active resistance to filling), such a sequence seems to indicate that blood was accumulating in the atrium at a faster rate than in the veins. This points to some factor causing hindrance to atrial emptying and this was evidently the rise in ventricular diastolic pressure.

Thus there were two *factors responsible for rise in atrial and venous pressure* in the experiments. One of these was the *increase in blood volume* which was the chief quantitative determinant, i.e., the chief factor responsible for the absolute values of venous pressure. The other was *alteration in blood distribution* with a relative shift toward the heart and away from the periphery. This was apparently the result of rise in ventricular diastolic pressure and was the chief qualitative determinant, i.e., the factor responsible for the difference in the degree of rise in pressure in the central and peripheral portions of the venous system. Since it has been amply demonstrated that increase in blood volume,[1, 12, 13] decrease in veno-atrial pressure difference,[3] and increase in ventricular diastolic pressure[14, 15] occur in patients with congestive heart failure, it would appear likely that the same quantitative and qualitative determinants of venous pressure are operative in such individuals. Whether or not a third factor, increase in venous tone, which has been thought to be operative in causing increase in venous pressure in patients with heart failure[16] was operative in these experiments is uncertain from the data.

*Some Possible Relationships between the Experimental Findings and Heart Failure in Patients*

It is now generally agreed that while most patients with congestive heart failure exhibit decline in the cardiac output per minute, this function may be normal or even increased.[2, 3, 17] Hence the old conception that the manifestations of heart failure are to be ascribed to absolute decline in output is no longer considered valid. However, the idea that heart failure is necessarily associated with inadequacy of output relative to the needs of the body[17, 18] is widely accepted and is supported by much recent evidence.

Inadequacy of cardiac output relative to metabolic needs cannot be considered the fundamental hemodynamic disturbance responsible for heart failure produced by massive infusion. Here heart failure is accompanied not only by absolute increase in cardiac output but also by increase in output relative to oxygen consumption. Two alternative conclusions are possible. The first is that heart failure is of more than one basic type and that the different types have fundamentally different mechanisms. The second is that there may be a mechanism common to all heart failure but that this mechanism is not inadequacy of cardiac output relative to metabolic needs. The latter hypothesis may now be considered.

It has been pointed out that experimental hypervolemic heart failure (table 1, fig. 2) was regularly associated with inadequacy of cardiac output relative to inflow load and evidence has been cited for the opinion that the discrepancy was dependent on rise in ventricular diastolic pressure. The question arises as to whether similar mechanisms may be concerned in all types of heart failure.

Studies with the catheter method are in general agreement in indicating that right ventricular diastolic pressure is elevated in patients with systemic congestion.[3, 14, 15] Measurements of left ventricular pressure are as yet few but such as have been made have indicated elevation[19] in patients with pulmonary congestion and this is supported by the more numerous studies which have shown elevation of pulmonary arterial[20] and right ventricular systolic pressures[14] in such patients with left-sided heart failure. One might therefore be tempted to draw the conclusion that failure of the left and right sides of the heart is always associated with elevation of diastolic pressure in the corresponding ventricle. Such a conclusion would be true in most patients but would in all probability be incorrect when applied to heart failure in general.

The literature does not seem to contain any references to measurements of ventricular diastolic pressures in patients with advanced stenosis of the corresponding atrioventricular orifices. Nevertheless, there is good, although indirect, evidence that such pressures are not elevated and may actually be reduced. In contrast to the marked dilatation and hypertrophy of the remaining cardiac chambers the left ventricle is sometimes found to be small and atrophic in patients with advanced mitral stenosis. Since it is very unlikely that the left ventricular diastolic pressure could be elevated in such patients, the concept of elevation of ventricular diastolic pressure as the least common denominator and the sine qua non of all heart failure is untenable.

Atrial pressure is of course elevated in patients with mitral and tricuspid stenosis and one might be tempted to conclude that elevation of atrial pressure is present in all patients with heart failure. However, such is not necessarily the case in patients with combined failure of the heart and periphery. It is probably true that in the absence of coexisting peripheral failure (such as may result from excessive sodium depletion) heart failure is always associated with elevation of atrial pressure, but it would not be correct to say that the presence of such elevation is an absolute necessity for heart failure.

It has been pointed out that heart failure produced by experimental hypervolemia is characterized by inadequacy of output in relation to inflow load. Although complete data are not available, such data as exist concerning cardiac output, venous pressure, atrial pressure, intrathoracic blood volume, and size of the great veins as observed at the bedside and at the autopsy table suggest that a similar inadequacy exists in all instances of clinical heart failure.* The same discrepancy is found in that appearing in the heart-lung preparation whether occurring spontaneously or dependent on excessive peripheral resistance or due to excessive elevation of the venous reservoir. The same discrepancy exists when heart failure appears suddenly as the result of temporary or lasting disturbances of rhythm; although quantitative studies are lacking, the clinical evidence of reduction in output despite prominence of the neck veins appears conclusive in these circumstances.

Increase in inflow load alone cannot be regarded as evidence of heart failure, for this occurs in normal persons during physical exercise and apparently in many diseases such as febrile illnesses, thyrotoxicosis, and anemia.†

* Since heart failure due to severe anemia may be accompanied by decline rather than increase in blood volume,[5] it might be considered that the inflow load is not increased under such circumstances. However, the inflow load is related not to the total blood volume but to the volume of blood in the great veins and these are distended in such patients, as has been pointed out by McMichael.[16] The active constriction of the peripheral venocapillary bed which appears to be present in patients with severe anemia[5] apparently tends to increase inflow load by causing a shift of blood to the central portions of the venous system.

† The evidence that inflow load is increased in these conditions is not based on quantitative measurements but on clinical findings of prominence of the large veins. The increase in cardiac output could

Decline in cardiac output alone does not signify heart failure for this is the classical hemodynamic disturbance of peripheral circulatory failure. The available evidence indicates, therefore, that the invariable and fundamental hemodynamic disturbance of heart failure is decline in output relative to inflow load or, conversely, elevation of inflow load in relation to cardiac output.

The question naturally arises as to whether, aside from the fundamental discrepancy between inflow load and output, the type of heart failure induced in animals by massive infusions bears any similarity to clinical states. Patients with acute nephritis and desoxycorticosterone intoxication may display the classical signs of increased cardiac output (accentuation of the heart sounds, moderate tachycardia, bounding pulse, elevation of pulse pressure) even when cardiac failure is present. However, such signs are not always encountered; other factors such as hypertension or myocardial lesions are usually present, and in any case actual measurements of cardiac output are lacking in such states. Heart failure is frequently precipitated in elderly subjects by the too zealous administration of fluids. In such instances the hypervolemia is rarely if ever the sole factor; pre-existing hypertension or senile heart disease is nearly always present even though asymptomatic.

The most common example of hypervolemia as a precipitating cause of heart failure is acute pulmonary edema. Such attacks are now believed to be in many instances due to the nocturnal reabsorption in the recumbent position of excess fluid accumulated during the day in the upright position.[21, 22] However, the hypervolemia is not the sole (or even the main) causative factor; valvular lesions, hypertension, or myocardial disease is always also present.

It will be evident from the foregoing discussion that primary hypervolemia, while a frequent cause of heart failure when occurring in conjunction with other cardiac disorders, rarely if ever causes heart failure in the absence of coexisting disturbances which either increase the burden on the myocardium or injure it directly.

Hypervolemia as a cause should not be confused with hypervolemia as a result of heart failure. Chronic congestive failure is usually associated with an increase in blood volume,[1, 12, 13] the mechanism of which remains obscure. This secondary hypervolemia may be compensatory in the sense of serving to elevate inflow load and hence to maintain cardiac output (provided the heart is in a functional state corresponding to the left or ascending limb of the Starling curve); it is also frequently harmful in tending to aggravate the congestive phenomena. The clinical improvement induced by reduction of blood volume consequent to venesection or diuretic drugs illustrates the harmful effects of this compensatory mechanism.

Primary hypervolemic heart failure is one example of the condition which McMichael and Sharpey-Schafer[5] have designated high-output failure. Other examples of high-output failure are disorders associated with primary disturbances in tissue oxidative processes (cor pulmonale with arterial anoxia, anemia, thyrotoxicosis, beriberi) and arteriovenous shunts. It would appear that the mechanism common to these several disorders is primary increase in inflow load.

*The Classification of Heart Failure*

*The clinical classification* into forward and backward types according to whether the dominant manifestations are mainly those of a shocklike state or of congestion has the advantages of simplicity and of often furnishing a guide to treatment. Among the disadvantages of such a classification are: (1) the confusion which may arise concerning forward failure because of the lack of comprehension of the distinction between the degree of systolic emptying and the actual stroke volume (see above), (2) the fact that all heart failure which is not complicated by coexistent peripheral failure is fundamentally backward in the sense of

also be induced by decline in peripheral resistance with consequent increased degree of systolic emptying, diminished residual blood, and reduction of ventricular diastolic pressure. The relative importance of the two mechanisms in causing the rise in cardiac output is uncertain at present.

TABLE 2.—*Classification of the General Circulatory Disorders*

| Fundamental Mechanisms | Common Synonyms | Major Subgroups | Examples | Remarks |
|---|---|---|---|---|
| | | A. *Primary Disorders of Cardiac Filling* | | |
| I. Primary deficiency of inflow load | Peripheral circulatory failure. Shock | 1. Defective blood volume (hematogenic shock) | Hemorrhage, trauma, dehydration | Blood volume too small for peripheral vascular bed, consequent deficiency of venous return |
| | | 2. Increased size of peripheral bed (neurogenic and vasogenic shock) | Emotional syncope, postural syncope | |
| II. Primary excess of inflow load with adequate systolic emptying | Overactive heart. Hyperkinetic syndrome. | 1. Disturbances in tissue oxidative processes | Thyrotoxicosis, anemia, beriberi, | Elevation of inflow load with parallel elevation of cardiac output |
| | | 2. Arteriovenous shunts | A-V fistula, patent ductus arteriosus | |
| | | 3. Primary hypervolemia | Acute nephritis, rapid infusions | |
| III. Primary excess of inflow load with inadequate systolic emptying | High output failure | As above | As above. Also many instances of acute pulmonary edema | Elevation of inflow load without corresponding elevation of cardiac output. (Myocardial disease or resistance to emptying usually also present) |
| IV. Mechanical hindrance to ventricular filling | Mechanical (i.e., nonmyocardial) heart failure | 1. Cardiac Tamponade | Pericardial effusion<br>Constrictive pericarditis | Digitalis resistant heart failure |
| | | 2. Stenosis of atrioventricular valves | Mitral stenosis | |
| | | 3. Rarer conditions | Ball valve thrombus<br>Auricular tumors | |
| | | B. *Primary Disorders of Cardiac Emptying* | | |
| I. Primary increase in resistance | | | | |
| a. Rapid onset without secondary hypervolemia | | Acute cor pulmonale | Pulmonary embolism | Collapse marked; congestion slight |
| b. Slow onset with secondary hypervolemia | | 1. Resistance at semilunar orifices | Aortic stenosis | Congestion marked; collapse absent or minimal |
| | | 2. Resistance in aorta | Coarctation | |
| | | 3. Resistance in arterioles | Hypertension | |
| II. Primary decline in myocardial function | | | | |
| a. Rapid onset without secondary hypervolemia | Sudden death | 1. Asystole | Ventricular fibrillation or standstill | Forward failure of the heart; collapse marked, congestion slight |
| | Cardiac syncope | 2. Sudden bradycardia | Adams-Stokes seizures<br>Carotid sinus syncope | |
| | Cardiac collapse | 3. Ectopic tachycardia | Auricular fibrillation | |
| | | 4. Acute myocardial injury | Myocardial infarction | |

TABLE 2—*Concluded*

| Fundamental Mechanisms | Common Synonyms | Major Subgroups | Examples | Remarks |
|---|---|---|---|---|
| b. Slow onset with secondary hypervolemia | Myocardial insufficiency; classical heart failure | 1. Inflammatory<br>2. Degenerative | Myocarditis<br>Senile heart disease; coronary arteriosclerosis | Backward failure; congestion marked; collapse minimal or absent |
| C. *Mixed Types* | | | | |
| Defective filling of one ventricle with defective emptying of the other | | | Mitral stenosis | Examples only; other mixed types occur. |
| Excess inflow load on one ventricle with defective emptying of the other | | | Aortic insufficiency | |
| Deficient systolic emptying plus deficient inflow load | | | Heart failure with excessive sodium depletion | |

elevation of atrial pressure, (3) the mistaken assumption that the term backward failure implies that the congestive phenomena are entirely the direct result of "back pressure" when actually hypervolemia is the more important cause, and (4) the coexistence of the two states.

The *topographic classification* of heart failure recognizes pericardial (tamponade), myocardial, and endocardial types. The difficulty with this classification is that while the pericardial and myocardial types each have distinctive mechanisms (primary failure of diastolic filling and primary failure of systolic emptying, respectively) no such unity exists for the various disorders of the endocardium. Thus resistance to emptying, excessive filling, and resistance to filling represent the essential mechanisms of aortic stenosis, aortic insufficiency and mitral stenosis, respectively.

A *physiologic classification* of heart failure should have the advantage of emphasizing the fundamental mechanisms and hence of furnishing a guide to management. Such a classification based on the general principles which have been discussed in this communication is presented in table 2. For the sake of clarity the other major general disturbances of the circulation are included, but disturbances involving local areas only (hemorrhage, thrombosis, embolism, and the like) are omitted. It should be noted that the classification as presented in table 2 is not all-inclusive. Thus primary deficiency of inflow load (A.I., table 2) could be subdivided into: (1) with adequacy of systolic emptying (i.e., the usual types of peripheral failure when not complicated by myocardial failure) and (2) without adequacy of systolic emptying (i.e., advanced peripheral failure complicated by heart failure as the result of prolonged deficiency of coronary flow). Similarly there should theoretically be a disorder characterized by primary excess of cardiac emptying. Definitive evidence that such a disorder exists is lacking.

The starting point of this discussion was the observation that heart failure may exist independently of absolute decline in cardiac output or of decline relative to the metabolic needs. It was pointed out that in the absence of coexisting disorders of the peripheral circulation myocardial failure is always associated with elevation of ventricular diastolic pressure and consequent elevation of atrial pressure. This elevation of ventricular diastolic pressure is due to incomplete systolic emptying which is commonly caused by a decline in stroke volume. However, under certain conditions (e.g., primary increase in inflow load as exemplified by heart failure due to excessive infusion) the decline in systolic emptying may occur despite a normal or elevated level of stroke volume. The sine qua non of myocardial failure is therefore to be found not in the cardiac output but in the completeness of the cardiac

emptying, i.e., in the degree of dilatation and the degree of rise in the intracardiac pressures.*

All heart failure is not myocardial, however. When the pericardium is at fault, the defect is not in emptying but in filling and the rise in pressure in the ventricle presumably first appears not at the beginning but at the end of diastole. When certain types of endocardial disease (stenosis of the atrioventricular valves) are present, the atrial pressure may be elevated despite normal or low values for the ventricular diastolic pressure. The conclusion that increased atrial pressure is invariably present in heart failure is, however, invalid; such need not be the case when cardiac and peripheral failure coexist.

All of the available information, whether obtained by quantitative measurement or by simple clinical observation, indicates that these various types of heart failure are uniformly attended by defective output in relation to inflow load. This concept appears to be equally applicable to the heart-lung preparation, to the patient dying suddenly of ventricular fibrillation, to individuals with acute or chronic congestive heart failure. Pending additional and more complete knowledge it appears justifiable to define heart failure as a condition in which the cardiac output is inadequate in relation to the filling load.

## Summary

1. A group of experiments is described in which dogs were infused rapidly with large volumes of fluid. The atrial and femoral venous pressures rose steadily during infusion; the cardiac output rose to a peak and then dropped. The gradient of pressure along the veins decreased progressively during the infusion.

2. It is concluded that the hemodynamic defect in primary hypervolemic heart failure is the heart's inability to respond to an increasing filling load beyond a certain point.

3. Filling in the heart-lung preparation is contrasted to that of the whole animal. From considerations concerned with the flow of fluids through tubes it is concluded that the diameter of the veins has more influence than the venous pressure on volume flow, and that the intact animal differs from Starling's heart-lung preparation not only in respect to varying peripheral resistance but also in that the veins may vary in diameter. This is illustrated by the experiments in which only a rough correlation exists between venous pressure and cardiac output. It is suggested that the concept of inflow load, incorporating venous pressure and venous diameter, supplant that of venous pressure as the stimulus to changes in stroke output of the heart.

4. The actual flow into the ventricle depends on the relationship between the inflow load and the ventricular diastolic pressure. Thus a decline in the latter function may occur when diminished peripheral resistance leads to increased systolic emptying and under such circumstances increased inflow and output may occur with constant inflow load.

5. It is pointed out that if ventricular diastolic pressure rises, the inflow load must increase to keep the inflow and output the same. In addition, it is emphasized that rise of ventricular diastolic pressure is a consequence of incomplete emptying of the ventricle and excessive residual blood, and that this may occur not only when the cardiac output is low but also when the cardiac output is high. It is suggested that the only hemodynamic disturbance constant to all types of heart failure is that the cardiac output is reduced relative to the inflow load.

6. It is pointed out that hypervolemia may be either primary and a cause of cardiac failure or, much more commonly, secondary and a result of heart failure.

7. The point is made that in states of myocardial failure the rise in ventricular diastolic pressure necessarily results in a distributional shift of blood from the peripheral toward the central portions of the venous system.

8. The relationship between blood volume

* There is strong evidence[11, 16] that the normal ventricles do not empty completely. The question of the degree of incompleteness, i.e., the amount of residual blood necessary to produce rise in ventricular diastolic pressure and secondary decline in filling, is one concerning which there is no exact information. Clinical experience would suggest that gallop and detectable dilatation by x-ray examination may be early indications of rise in ventricular diastolic pressure but quantitative data are lacking.

and venous pressure is considered. If venous tone remains constant, the venous pressure is determined by total blood volume and by blood distribution.

9. On the basis of these considerations a physiologic classification of heart failure and other circulatory disturbances is presented. This classification attempts to consider the circulatory disturbances from the standpoint of primary alterations in filling and emptying of the heart respectively.

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# Catheterization of the Left Side of the Heart in Man

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The technic employed in catheterization of the left heart in man is described. A catheter is introduced into the left ulnar artery and passed through the brachial, axillary and subclavian arteries into the arch of the aorta. With the tip of the catheter at the root of the aorta, we have succeeded in entering the left ventricle only in patients with free aortic insufficiency due to syphilis. Failure to pass the aortic valves in normal subjects is discussed.

SINCE the earlier work of Cournand and Ranges,[1] Stead and his associates,[2] McMichael and Sharpey-Schafer,[3] and others, catheterization of the right ventricle and pulmonary artery in man has become a standard procedure which not only supplies valuable data in the accurate diagnosis of congenitally malformed hearts, but which is also applicable to the study of a variety of problems in the cardiovascular field. A considerable experience with catheterization of the right side of the heart prompted us to try the procedure on the left side.

Catheterization of the left side of the heart presents obvious problems not encountered on the right side. The catheter must move retrograde against arterial pressure while arterial vasospasm may be so marked that the catheter cannot be passed forward. After reaching the aortic root it must be moved through the orifice into the left ventricle against the blood column and in that short ejection interval (0.22 second) during which the aortic valves are open.

The exact position of normal aortic leaflets during ventricular systole in the intact heart is not known. If the pressure difference in the left ventricle and aorta were the only factors concerned the valves would lie snugly against the intima of the aorta, but other subsidiary forces may actually move the valve toward a position of closure during the ejection phase.

As Wiggers[4] has stated, "Among these accessory forces, two deserve consideration: (1) the production of a turbulent flow with the formation of eddies behind the valves, thus supplying the force by which they may be partially closed during the process of ejection, and (2) the negative pressure which develops in the axial stream when a jet is suddenly stopped. Into this area of negative pressure, fluid is drawn from the sides much as water into the wake of a ship and the valves are carried with the blood."

That the normal aortic orifice may not be "wide open" during systole is suggested by the fact that to date we have been unable to bypass the valves and enter the left ventricle in five normal subjects. The axial aortic pressure probably forces the catheter tip to the side, and as it moves toward the orifice it enters the sinus of Valsalva. In a person with free aortic insufficiency, particularly that due to syphilis, the possibility of entering the left ventricle would appear to be much better than in the normal subject and this has proved to be the case.

## TECHNIC

The ulnar artery was selected for the introduction of the catheter because of its size; it is readily accessible and if necessary may be ligated with impunity. The artery is exposed at the juncture of its upper and middle third which is 8 to 9 cm. distal to the medial epicondyle of the humerus. Here the artery is just beneath the flexor carpi ulnaris muscle and lies on the flexor profundus digitorum with the ulnar nerve parallel and medial. With the left arm supinated, the operative field is infiltrated with a 1 per cent solution of procaine. A 2-cm. incision is made parallel to the median border of the flexor carpi ulnaris and carried through

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the skin and superficial fascia. The dissection is made obliquely inward toward the ulna and the nerve and artery are readily exposed. The periarterial tissue is now infiltrated with a 1 per cent solution of procaine and the vessel completely isolated. Proximally and distally to the site of the opening are placed two small umbilical tapes to control hemorrhage.

A catheter corresponding in size to the artery (usually a no. 6 intracardiac catheter) is selected, and a stylet is inserted according to the technic of Bing,[5] taking care that the stylet is about 2 mm. from the catheter tip. The catheter is then well lubricated with sterile olive oil and filled with a 0.01 per cent solution of heparin in normal saline. A continuous flow of the heparin solution (20 to 30 minims per minute) is maintained through the catheter by means of a specially designed electric pressure pump, except at such times as pressures are being recorded or blood samples are being withdrawn. A 3 to 4-mm. longitudinal incision is made in the arterial wall through which the catheter is introduced and under the fluoroscope passed at once through the brachial, axillary, and subclavian arteries and into the arch of the aorta. In some cases we were able with one motion to pass the catheter from the ulnar artery into the cavity of the left ventricle. The quicker and smoother the catheter is moved forward, the less difficulty one has with vasospasm and, once the catheter is completely withdrawn, further attempts to reintroduce it are usually unsuccessful. Failure to pass the catheter beyond the junction of the subclavian artery with the aortic arch occurred in 20 per cent of our patients with aortic insufficiency, but having entered the ascending aorta to the level of the aortic valves, failure to pass the orifice into the cavity of the left ventricle has occurred in only three instances. When the catheter tip reaches the aortic root the heparin solution is replaced by the patient's heparinized blood until the cavity of the left ventricle is entered.

After the desirable data are recorded, the catheter is withdrawn and the incision in the ulnar artery is closed with interrupted 6–0 Deknatel sutures. The fascia and skin are closed with interrupted, black silk sutures and a light pressure dressing is applied. In one patient we were unable to repair the ulnar artery and were forced to ligate it but no untoward effects resulted. Immediately following catheterization the patient is given 75 mg. heparin intramuscularly every six hours for three days.

## Results

In 11 patients with syphilitic aortic insufficiency we have succeeded in reaching the cavity of the left ventricle with no untoward complications. Figure 1 shows the position of the catheter in both the left and right side of the heart in the same patient. In one patient with rheumatic aortic insufficiency, during the attempt to move the catheter into the left ventricle, the subject suddenly complained of substernal pain and the electrocardiogram which was being recorded showed the abrupt appearance of ventricular fibrillation. The catheter was immediately withdrawn. Nine cubic centimeters of 1 per cent solution of procaine with 0.5 cc. of a 1:1000 solution of adrenalin were injected directly into the heart without effect on the cardiac mechanism. The heart was then exposed and massaged. This resulted in the restoration of a sinus rhythm, but the ventric-

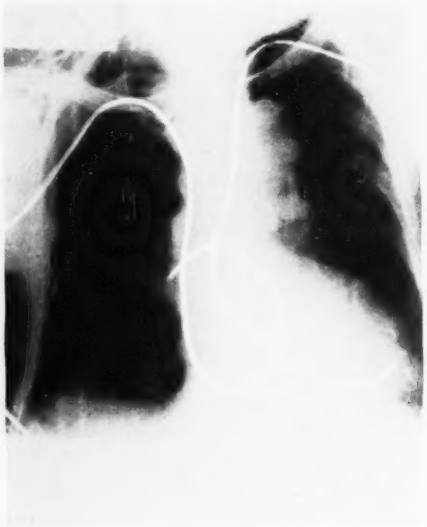

Fig. 1.—An x-ray photograph showing the position of the catheters in both sides of the heart.

ular contractions were feeble and fifteen minutes after the onset of ventricular fibrillation the heart ceased beating. At autopsy, the heart weighed 550 grams and exhibited a rheumatic scarred mitral and aortic valve, the latter being fused and retracted. A careful search was made for any evidence of trauma to the root of the aorta, the aortic valves, or coronary ostia, but none was found. The ostium of the left coronary artery was anomalous in that it was situated 3 mm. above the normal site. The circumstances under which the patient expired naturally led to the assumption that the catheter had entered and partially or completely blocked the ostium of a coronary artery, presumably the left coronary, resulting in ventricular fibrillation. Histologic sections of the myocardium showed active rheumatic inflammation with many Aschoff bodies which probably lowered the threshold for the induction of ventricular fibrillation in this heart.

In a patient who died four days after catheterization from congestive failure, a careful search post mortem revealed no evidence of trauma of the aorta, aortic valves, or endocardium of the left ventricle. In one patient, premature ventricular contractions and in another, short runs of ventricular tachycardia occurred, but in both, a sinus rhythm was restored by moving the tip of the catheter.

## Summary

A method for the catheterization of the left ventricle in man is described. The left ventricle was entered in 11 patients with syphilitic aortic insufficiency with no untoward results but one patient with rheumatic aortic insufficiency and active rheumatic myocarditis succumbed from ventricular fibrillation.

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# Dissecting Aneurysm of the Aorta: Its Clinical, Electrocardiographic and Laboratory Features

## A Report of Fifty-eight Autopsied Cases

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The literature has been reviewed, and 58 autopsied cases of dissecting aneurysm of the aorta observed at the Los Angeles County Hospital over a ten year period have been carefully studied. Clinical-pathologic correlation has been attempted whenever possible, with emphasis on diagnostic features. The increasing incidence of accurate diagnosis of dissecting aneurysm has been noted, and it is hoped that this review will help solidify the clinical syndrome or syndromes of the condition and thus facilitate diagnosis in dubious instances.

DESPITE the recent excellent reviews and publication of case reports of dissecting aneurysm by David, McPeak, Vivas-Salas, and White,[1] Leitch,[2] Sailer,[3] and others, it was felt that by reviewing a relatively large series of cases some valuable data might be uncovered. The diversity of symptoms in the clinical syndromes presented by dissecting aneurysm cannot be overemphasized if the percentage of correct antemortem diagnosis is to be increased. The importance of a correct diagnosis may grow if surgical treatment should prove effective. Secondly, the mechanism behind the occurrence of the diastolic murmur needs further study. Finally, the electrocardiogram hitherto has been said to show either normal or nonspecific tracings, and it was felt that these were statements which needed further clarification in view of the known courses of dissection in this disease.

### Historical Background

Dissecting aneurysm is the lesion produced by the penetration of circulating blood into the wall of the aorta, and subsequent extension for a varying distance resulting in a separation of the layers of the vessel wall. An intravascular hematoma may arise from hemorrhage of the vasa vasorum, and have no communication with the lumen of the vessel, or the hematoma may communicate with the lumen of the vessel through one or more intimal tears. Commonly, rupture occurs either back into the lumen via an intimal tear, or into the exterior by perforation of the adventitia.

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Vesalius,[4] in 1557, was the first to diagnose an aneurysm. This aneurysm occurred in a man who developed a pulsating abdominal tumor after falling off a horse. Sennertus,[5] in 1628, maintained that the immediate cause of an aneurysm was the rupture of the internal coat with elevation and distention of the external coat. This was supported by Scarpa[6] in 1804. Nicholls,[7] in 1763, in reporting the cause of death of King George II, which occurred while straining at stool, described an aneurysm within the coats of the aorta, accompanied by a large intimal tear and rupture into the right ventricle. He attributed this to the greatly increased intravascular pressure at the time of death. Morgagni,[8] in 1760, cited the above case, and reported several cases of his own in which the blood had made its way by degrees through the vessel wall. Maunoir,[9] in 1802, first clearly described dissection of the arterial coats by blood. Laennec,[10] seventeen years after Maunoir, also described this condition, and was the first to use the term "aneurysme dissequant." Unfortunately, much of the credit belonging to Maunoir has been given to Laennec. Shekelton,[11] in 1822, was the first to describe "healed" dissecting aneurysm in which there was re-entry at a lower level in the aorta, allowing circulation of blood through the false sac. Pennock,[12] in 1839, described the first case recorded in the American literature, and demonstrated that dissection takes place in the laminae of the media. As early as 1855, Swaine, Keyworth, and Latham[13] reported the first case of dissecting aneurysm to be diagnosed correctly antemortem.

### Incidence

The recent literature was reviewed, and records of approximately 734 cases of dissecting aneurysm of the aorta were found. In 88 (10.6 per cent) of these cases a correct antemortem diagnosis had been made. Shennan,[14] who reviewed the literature up to 1933, was able to collect 317 cases, of which only 6 (1.8 per cent)

were correctly diagnosed antemortem. The present report is based on the study of 58 cases of dissecting aneurysm demonstrated at autopsy at the Los Angeles County Hospital from 1935 to 1947, inclusive. Of this group, a correct antemortem diagnosis was made in 16 instances (27.5 per cent). During the same period, there were 18 cases in which dissection localized to the abdominal aorta was found at necropsy. These cases will be the subject of a future report.

*Autopsy Incidence.* The autopsy incidence of dissecting aneurysm at the Los Angeles County Hospital from 1935 to 1947, inclusive, was one in 447 subjects. David, McPeak, Vivas-Salas, and White[1] reported an incidence of one in 128 autopsy subjects at the Massachusetts General Hospital from 1937 to 1946. A recent review by Warren and McQuown[15] disclosed an autopsy incidence of one in 450 subjects at the Charity Hospital. Their findings were almost identical in this respect to those of the present study. McGeachy and Paullin,[16] in 1937, reported an autopsy incidence of one in 500 subjects. Flaxman,[17] in 1942, found one dissecting aneurysm in every 714 autopsy subjects at the Cook County Hospital. That these figures may be misleading was evidenced by the excellent report of Mote and Carr,[18] who reported 60 cases of dissecting aneurysm during autopsy examinations by the San Francisco Coroner's Office over a five-year period (1933–1937). This greatly exceeded the incidence of dissecting aneurysms in other hospital examinations in San Francisco over the same period. This report confirms the suspicion that dissection often occurs without antecedent history or warning, resulting in death within minutes to hours, and also, that the actual incidence of this entity is much more frequent than one is led to believe from the various autopsy statistics, most of which come from large general hospitals.

*Age Incidence.* The greatest frequency of dissecting aneurysms (table 1) occurred in persons between the fifth and seventh decades of life. Thirty-six of the 58 cases occurred during this period. The oldest patient was a 90 year old Negro, and the youngest, a 22 year old Negro. The oldest patient whose record was found in the literature was a 100 year old woman, and the youngest a 14 month old infant. Schnitker and Bayer[19] were impressed with the frequency of this condition among young people. They reviewed the literature to 1943, and found that of the total number of cases reported, 24 per cent occurred in individuals under 40 years of age. In the present series, there were only 6 cases (10 per cent) in persons under the age of 40 years. This discrepancy can be explained in part by the large older-age population found in the Los Angeles area.

*Sex Incidence.* The ratio of men to women is usually reported as men predominating two to three times as frequently as women. In the group being reported, the incidence in men was found to be about 2.6 times as frequent as that in women. In the 60 subjects seen at the Coroner's Office in San Francisco,[18] there were 52 men and only 8 women, the incidence in the men being 6.5 times as frequent as that in the women. Whether this implies that men are more apt to die suddenly than women who have this condition is purely a matter of speculation.

TABLE 1.—*Age, Sex and Race Distribution of Fifty-Eight Cases of Dissecting Aneurysm (1935–47 Inclusive)*

| Age (Years) | Male | | | Female | |
|---|---|---|---|---|---|
| | White | Negro | Chinese | White | Negro |
| 0–10 | | | | | |
| 11–20 | | | | | |
| 21–30 | 1 | 1 | | 1 | |
| 31–40 | 1 | 1 | | 1 | |
| 41–50 | 2 | | | 2 | 1 |
| 51–60 | 8 | 5 | 1 | 3 | |
| 61–70 | 12 | 3 | | 3 | 1 |
| 71–80 | 5 | | | 2 | 1 |
| 81–90 | 1 | 1 | | | 1 |
| Total | 30 | 11 | 1 | 12 | 4 |
| Total | 42 | | | 16 | |

The average age for women was found to be 58 years, and that of men 59.9 years. This is not the usual or, rather, expected finding. The women usually dominate the older-age brackets. The average age in David, McPeak, Vivas-Salas, and White's[1] report was women—63 years, and men—58 years. The delayed onset of hypertension in women would lead one to

suspect that the average age of women with dissecting aneurysms should exceed that of men. An interesting observation by Schnitker and Bayer[19] was that in those cases occurring in women under the age of 40, 50 per cent were found to be in association with pregnancy.

*Race Incidence.* Of the 58 cases, 15 (25.8 per cent) occurred in Negroes. There was no unusual distribution of sex within the races, the men predominating in both races 2.6 to 1. The high percentage of Negroes is not remarkable in light of the fact that hypertension is known to occur twice as frequently among Negroes as among white persons. There was one case worthy of special mention which was found in a 50 year old Chinese, hypertension being reported as unusual in the Chinese race. We were unable to find any other reports in the literature of a dissecting aneurysm occurring in a Chinese.

## Clinical Classification

In 1929, Gager[20] proposed a classification of dissecting aneurysms, concerned primarily with the duration of survival. Such a classification is particularly applicable to this entity, and with modifications, it is presented as follows:

*Acute Type.* Rupture of the intima, dissection of the media, and terminal perforation of the adventitia into a viscus such as the pericardial cavity, pleural cavity, and mediastinum, takes place within minutes to hours, resulting in death within twenty-four to forty-eight hours after the initial onset. Case 1 has been chosen as being illustrative of this type.

*Case 1.* Two hours prior to hospital admission on November 12, 1945, this 46 year old white man had a sudden onset of "constriction" about his chest which lasted about fifteen minutes, and which was soon replaced by an intense, sharp, epigastric pain.

The patient was well developed. He was tossing about in bed and complained of pain. His extremities were cold and clammy. His temperature was 97 F. The pulse rate was 88 per minute and respiratory rate 34 per minute. The lungs were clear. There was no cardiac enlargement or heart murmurs. The blood pressure was 175/100. Epigastric and left upper-quadrant tenderness was present.

The urinalysis showed no abnormality. The Wassermann and Kahn reactions were negative. A flat plate of the abdomen showed no renal calculi.

The patient was discharged from the hospital on Nov. 14, 1945.

On Nov. 20, 1945, seven days after discharge, the patient was readmitted to the hospital. He complained of severe epigastric pain and vomiting. The pain had come on while he was asleep, and was severe, steady, and localized to the epigastrium.

At the time of examination the patient was thrashing about and groaning loudly. His temperature was 97.5 F.; the pulse rate was 100 per minute and respiratory rate 34 per minute. The lungs were clear. The heart did not appear enlarged, and the sounds were distant. The blood pressure was 90/50. Epigastric tenderness was present.

The electrocardiogram showed abnormal tracings in that the RS-T segments in Leads I, II, and III were depressed.

Five hours after being admitted in shock, the patient suddenly expired.

The postmortem findings were as follows: The pericardium was normal. The heart weighed 500 grams. The coronary vessels were markedly atherosclerotic but showed no occlusion. The valves were thin and measured: aortic, 8 cm.; pulmonic, 7.5 cm.; tricuspid, 14 cm.; mitral, 12 centimeters. The aorta had a few atherosclerotic plaques, and in the first portion of the arch of the aorta there was a transverse intimal tear which communicated with a dissecting aneurysm. The aneurysm extended distally to the level of the diaphragm, and was filled with recently clotted blood. There were several areas of rupture in the adventitia of the thoracic aorta with resultant bleeding into the mediastinum and left pleural cavity. There was a massive blood clot in the left pleural cavity which weighed 1200 grams.

*Subacute Type.* In this group, the process of intimal rupture and medial dissection is protracted, occurring gradually over a period of days or weeks, during which time symptoms and signs appear which are readily localized and of value in making or confirming the diagnosis. In this group, after a period of slow but progressive dissection, almost always a terminal adventitial rupture occurs similar to that of the acute type, which invariably results in a fatal outcome. Case 2 is illustrative of this type of patient.

*Case 2.* The patient, a 65 year old known hypertensive man, admitted to the hospital on January 25, 1947, and died February 4, 1947. Four days prior to admission, he noticed the onset of severe, sharp pain in the lower portion of his chest, which came on at rest. It lasted about twelve hours, and migrated down into his abdomen. Since that time he had had intermittent pain in the lower part of his back and in his right flank, which was accompanied by frequency of urination, dysuria, and vomiting. In addition, he had been constipated for four days prior to admission.

On examination, the patient chiefly complained of pain in his right flank. His temperature was 100.2 F.; the pulse rate was 88 per minute and respiratory rate 18 per minute. There were a few scattered râles at both lung bases. The heart appeared enlarged to the left on percussion. There was a soft, systolic murmur present over the entire precordium, best heard at the apex. The blood pressure was 190/100. There was deep tenderness in both upper quadrants of the abdomen. Bilateral costovertebral-angle tenderness was present. A bruit was heard just to the right of the umbilicus anteriorly.

The hemoglobin value was 16 grams, and there were 9,500 white blood cells per cu. mm. of blood. The urinalysis showed no trace of albumin. The nonprotein nitrogen was 70 mg. per 100 cc. of blood. Wassermann and Kahn reactions were negative. At fluoroscopy, the aorta was found to be dilated in the ascending and transverse portions of the arch, and the left border of the aorta was shaggy and irregular with diminished pulsations. The left ventricle was moderately enlarged. The findings were thought to be consistent with the diagnosis of a dissecting aneurysm. The electrocardiogram showed abnormality. The RS-T segment in Lead I was sagging and depressed. The Q-T interval was 0.44 seconds.

The course was febrile with daily elevation of temperature to 100 F. Intermittent pain in the right flank, and deep abdominal tenderness persisted. An aortic diastolic murmur appeared. During his ninth hospital day the patient became distended, anuric, and finally expired.

The antemortem diagnosis was dissecting aneurysm.

The postmortem findings were as follows: The pericardium was normal and contained 250 cc. of a straw-colored fluid. The heart was enlarged and weighed 570 grams. The valves were normal; the aortic measured 7 cm. and the pulmonic, 7.5 centimeters. The left ventricle measured 16 mm., and the right 2 to 4 millimeters. There was a dissecting aneurysm which originated at the level of the innominate artery and extended distally for about 2 cm. into both common iliacs. There was a large intimal tear 4 cm. proximal to the celiac axis. In the region of the renal arteries, the dilated aneurysmal sac partially occluded the left renal artery and completely occluded the right. There were large antemortem thrombi which occluded both renal stoma and entered both renal arteries for a distance of 7 millimeters.

The right kidney was a small, soft, pale organ approximately half the size of the left (combined weight of both kidneys—250 grams). The cut surface of the right kidney revealed markedly pale cortical and pyramidal structures. There was a large, yellow area which extended through the entire cortex to the pelvis. The left kidney was also pale, but appeared more normal than the right. The capsules of both kidneys striped with ease.

Microscopic examination of the aorta showed that medial degeneration and cyst formation were present.

The right kidney showed necrosis and fatty degeneration of the tubules, and interstitial hemorrhage typical of infarction.

*Chronic or "Healed" Type.* This group includes patients who survive the initial dissection. Healing is made possible by either reentry of the dissected passage into the lumen of the aorta or into the common iliacs, with subsequent endothelialization of the false passage and the establishment of a "double-barrelled" aorta. Or, less frequently, healing may take place by obliteration of the false passage by clot formation with subsequent organization and replacement fibrosis. Patients with "healed" dissecting aneurysms may survive for months or years, and death usually occurs in one of several manners. Most commonly, it is due to congestive failure, a cerebral accident, coronary artery disease, or other incidental illnesses. In a small percentage a second dissection occurs followed by fatal perforation. Case 3 has been chosen as best illustrating this type of course.

*Case 3.* The patient, a 62 year old white man, a confectioner, was admitted to the hospital on December 11, 1933, complaining of severe pain in his back, radiating to his arms and legs, and accompanied by dyspnea and vomiting.

On examination he appeared to be in acute distress. His temperature was 98.6 F. His pulse rate was 100 per minute and his respiratory rate 24 per minute. There were moist râles at the base of the left lung. The heart was not enlarged. A mitral systolic murmur was present. The blood pressure was 175/100.

The electrocardiogram showed left ventricular hypertrophy. The Wassermann and Kahn reactions were negative.

Shortly after admission, the patient became free of pain, and on his seventh hospital day, December 18, 1933, he was discharged to the Outpatient Department with the diagnosis of hypertension and coronary artery disease.

He was readmitted to the hospital on September 29, 1939, in congestive heart failure, complaining of dyspnea on exertion, paroxysmal nocturnal dyspnea, and precordial pain of three months' duration.

The patient was well developed. He was dyspneic, orthopneic, and slightly cyanotic. His temperature was 97.6 F. The pulse rate was 100 per minute, and

respiratory rate 22 per minute. The lungs were clear. The heart was enlarged, and the point of maximal impulse was felt in the fifth intercostal space at the anterior axillary line. Aortic systolic and diastolic murmurs were present. The blood pressure in the right arm was 200/100, and in the left arm, 190/100. The physical examination revealed no abnormality other than that pertaining to the heart.

The Wassermann and Kahn reactions were negative. The electrocardiogram again showed left ventricular hypertrophy. The orthodiagram showed marked fusiform dilatation of the ascending aorta, with moderate enlargement of the left ventricle. The innominate artery also appeared dilated.

The patient was treated with bed rest, restricted fluids, and digitalis. He improved gradually. Nine days after admission he was discharged to the Outpatient Department.

The significant findings on this admission were the detection of an aortic diastolic murmur, with aneurysmal dilatation of the ascending aorta, and negative serologic reactions. Both the third and fourth admissions (July 28 to August 5, 1940, and January 1 to May 16, 1941) were because of congestive heart failure, and in both instances the response to digitalis and bed rest was satisfactory.

On the final admission, March 5, 1941, he complained of dyspnea, orthopnea and ankle edema of six days' duration.

At this time he was extremely dyspneic and orthopneic. His temperature was 98.5 F., the pulse rate was 80 per minute, and the respiratory rate 20 per minute. Dullness, diminished breath sounds, and tactile fremitus were found over the right lower lobe posteriorly. Moist râles were heard at the base of the left lung. The heart was enlarged, and the point of maximal impulse was in the sixth intercostal space at the anterior axillary line. Systolic and diastolic aortic murmurs were present. The blood pressure was 184/80. The liver was enlarged down to the level of the umbilicus. There was +4 pitting ankle edema. There were 4,000,000 erythrocytes per cu. mm. of blood. The hemoglobin value was 86 per cent. The white blood cells numbered 6,600 per cu. mm. of blood. The urinalysis showed no abnormality, and the nonprotein nitrogen value was 51 mg. per 100 cc. of blood. The electrocardiogram showed auricular fibrillation, left ventricular hypertrophy, and digitalis effect.

The patient was treated with bed rest, digitalis, diuretics, a low-salt diet, and allied measures. Despite vigorous therapy his condition became progressively worse, and he died May 16, 1941.

The postmortem findings were as follows: The visceral and parietal pericardium were adherent by easily separated adhesions. The heart weighed 700 grams. The valves were normal, except for fusion over an extent of 4 mm. between the posterior and right aortic valve cusps. There was no evidence of any rheumatic involvement. The aortic valve measured 8 cm. and the pulmonic, 7.5 centimeters. The left ventricle measured 17 mm., the right 6 millimeters. Approximately 5 cm. above the aortic ring there was a transverse intimal tear which communicated with the false sac of a dissecting aneurysm. The aneurysm extended proximally down into the aortic ring, and distally to the common iliacs, where re-entry occurred. The lining of the true passage was wrinkled and had some lipoid plaques. The false passage was lined with intima, was wrinkled and rough, and had almost a tree-bark appearance. The common innominate artery and the left subclavian artery had also been involved in the dissection.

The microscopic examination of the aorta showed medial necrosis with cyst formation.

## Duration of Survival

The 58 cases being reported consisted of 43 acute and subacute types, and 15 of the chronic or "healed" type. The duration of survival of the patients of each group has been tabulated in table 2.

TABLE 2.—*Duration of Survival of Fifty-Eight Patients with Dissecting Aneurysm*

| Dissecting Aneurysm | Duration of Survival | Number of Patients | Percentage of Total |
|---|---|---|---|
| "Acute" type | 1–48 hours | 21 | 36.2 |
| "Subacute" type | 3–10 days | 13 | 22.4 |
| | 11–60 days | 9 | 15.5 |
| "Chronic" or "healed" type | 3 months to 8 years | 15 | 25.9 |

About one-third of the total number of patients died within the first forty-eight hours, and about one-half within the first ten days. The fact that one-fourth of the patients had the chronic or "healed" type, surviving three months to eight years, is a much more encouraging finding than that of Weiss,[53] who found that healing occurred in about 10 per cent of the patients, chiefly by means of re-entry of the false passage into the true lumen at a lower level.

## Clinical Symptoms

*Presenting Symptoms or Mode of Onset.* Pain was the presenting symptom in 45 (77.6 per cent) of the 58 cases. It was located in the chest in 17 patients (29.3 per cent), and in the epigastrium in 14 (24.1 per cent). In the remaining patients the pain was described as being in both the epigastrium and lower chest

(4 patients), the interscapular region (4 patients), the neck (3 patients), the midback (2 patients), and the sacrum (1 patient). (See table 3.)

The sudden onset of pain, the type of pain, its location initially, and subsequent radiation, are all of utmost value in arriving at a correct diagnosis, and will all be discussed in some detail.

Onset of Pain: The pain was described as having had a sudden, dramatic, and acute onset, usually with no definite relation to effort or activity, except for several instances in which physical exertion may have been a precipitating factor. One case, interestingly, occurred in a 34 year old Negro during sexual intercourse. In this group of 58 cases, physical exertion was not an important factor in initiating the dissection, but, contrariwise, many of these cases came on while the patient was sleeping. Cherry and Cherry[21] carefully reviewed the antecedent activity and occupations of 77 patients with dissecting aneurysm, and arrived at the conclusion that physical exertion is not an important factor in the initiation of dissection, but rather that its occurrence is merely coincidental.

Type of Pain: The pain was most commonly described as being sudden, severe, tearing, ripping, sharp, excruciating, cramplike, or burning. Not infrequently it was so severe as to cause the patient to double up in bed, or to lie on the floor in an attempt to obtain relief. In some instances, the pain was so intense that the patient was unable to lie still, and tossed about in bed. It was not infrequently described as a sensation of "something having torn loose" in the chest, or as the feeling of a knife being stuck into the chest and then twisted. In only 2 cases was the pain described as being oppressive in nature, resembling that of acute myocardial infarction. Kilgore[22] described the pain as sometimes "throbbing," in synchrony with the heart beat, owing to successive pulse waves splitting the media or distending the newly formed wall.

Site of Pain: The most frequent location of pain in this series of patients was in the chest, where it was present in 17 patients (29.3 per cent of the total). David, McPeak, Vivas-Salas, and White[1] recorded the initial pain as being in the chest in 10 of 17 cases (58 per cent). Logue[23] reviewed a group of 12 cases, all diagnosed antemortem, and found the pain substernal in 6 (50 per cent). Because the chest is the commonest site of the initial pain, and because the error most frequently encountered is in mistaking dissecting aneurysms for acute myocardial infarction, the chest pain in the above 17 cases was closely scrutinized. It was described as being in the anterior midchest in 9 of these cases, substernal in 6, and merely in the "left chest" in the remaining 2. Of the 6 patients in whom it was described as being substernal, it was definitely aggravated by deep breathing in 2 patients (associated hemothorax

TABLE 3.—*Mode of Onset in Fifty-Eight Cases of Dissecting Aneurysm*

| Mode of Onset | Incidence | Percentage of Total |
|---|---|---|
| I. Pain | 45 | 77.6 |
| A. Chest | 17 | 29.3 |
| 1. Anterior mid-chest | 9 | |
| 2. Substernal | 6 | |
| 3. Left side of chest | 2 | |
| B. Epigastrium | 14 | 24.1 |
| C. Epigastrium and low in chest | 4 | |
| D. Interscapular | 4 | |
| E. Neck | 3 | |
| F. Midback | 2 | |
| G. Sacrum | 1 | |
| II. Syncope | 8 | 13.2 |
| III. No history of pain or syncope | 6 | 8.6 |

present), in 2 others it was said to be sharp and knifelike, and in only the remaining 2 was it described as being oppressive and crushing. So actually, in only 2 of the 17 cases, in which the pain originated in the chest, was there any real semblance to the pain of myocardial infarction.

The second commonest location of the initial pain was in the epigastrium or abdomen. Here the pain was described as being ripping, tearing, or cramplike, and was actually usually quite severe. The pain was present in the epigastrium initially in 14 (21.1 per cent) of the patients. The fact that approximately one-fourth of the dissecting aneurysms in this series had their onset with epigastric pain is most important, and recognition of this incidence should be of

value in making the correct diagnosis. Every patient with acute, severe epigastric pain and associated hypertension should be suspected of having a dissecting aneurysm as well as an acute abdomen. The readiness with which the diagnosis of dissecting aneurysm can be confused with that of an acute abdomen is well illustrated in the literature. Finkelstein and Jacobi[24] reported a case of dissecting aneurysm associated with epigastric pain radiating through to the back, in which the antemortem diagnosis had been that of a perforated peptic ulcer. Other cases have been misdiagnosed as acute peritonitis, mesenteric thrombosis, and acute pancreatitis. Further confusion is added to the picture by the fact that the dissection may involve the superior mesenteric artery, resulting in its occlusion and subsequent infarction of the intestine. Kennedy[25] described just such a case, in which the antemortem diagnosis had been mesenteric thrombosis. At necropsy a dissecting aneurysm involving the superior mesenteric artery was discovered.

The difficulty in this differential diagnosis is so marked that not infrequently these patients are subjected to abdominal surgery because they are thought to have an acute abdomen. Levitt, Levy, and Cole[26] tell of a patient sent to surgery for abdominal exploration, and a similar incident followed in one of our patients.

*Case 4.* The patient, a 59 year old white man, a laborer and a known hypertensive, entered the Los Angeles County Hospital on October 7, 1944, because of severe epigastric pain of several hours' duration. The pain radiated to the back and to both shoulders. He was acutely ill, and tossed about in bed because of severe abdominal pain. His temperature was 98 F. The pulse rate was 84 per minute.

The lungs were clear. The heart was enlarged and the point of maximal impulse was in the fifth intercostal space at the anterior axillary line. There was an apical systolic murmur and a diastolic murmur over the entire precordium. The blood pressure was 280/150. The abdomen was flat and did not move with respiration. There was boardlike rigidity in the upper quadrants and peristalsis was absent.

There were 10,000 white blood cells (polymorphonuclear neutrophils, 93 per cent; lymphocytes, 7 per cent) per cu. mm. of blood. The urinalysis showed +2 albumin reaction, one to seven erythrocytes per high-powered field, and several hyaline and granular casts. The blood amylase was 300 units (normal 80 to 150 units).

The admitting diagnosis was that of a perforated peptic ulcer with the secondary possibility of an acute pancreatitis. The patient was taken to the operating room several hours after admission and an exploratory laparotomy was performed. The findings at the operation were all negative except for dilatation of the small intestine. One hour after the operation, the patient suddenly expired.

The postmortem findings were as follows: The heart weighed 650 grams. The valves were normal; the aortic measured 9 cm., the pulmonic 8 centimeters. The wall of the left ventricle measured 20 mm., and that of the right ventricle 2 to 3 centimeters. Tree-barking and stellate scars were found in the first portion of the ascending aorta. At the level of the innominate artery there was a dissecting aneurysm which dissected distally down into both common iliacs. There were no intimal tears and no sites of external rupture. The dissection involved the innominate and superior mesenteric vessels.

There was marked dilatation of the stomach, and of both the large and small intestine. There were some areas of the small bowel in which the wall appeared somewhat hemorrhagic. There was also hemorrhage about the head of the pancreas. On sectioning, the pancreas did not appear abnormal.

The aorta showed medial necrosis and cyst formation on microscopic examination. Changes in the pancreas were minimal and were thought mostly to represent postmortem autolysis.

In 16 cases, the pain radiated to the back. Radiation was present in the chest in 7 patients in whom the initial pain occurred in the neck, chest, or intrascapular or similar areas.

Radiation into the flanks was described in 4 cases, and at necropsy this was found to have been due to dissection of one or both renal arteries, resulting in partial or complete occlusion and renal infarction. Blain, Glynn, and Hiratzka[27] noted flank pain simulating that of renal colic in 2 patients, in both of whom the renal arteries were involved in the dissection. They reviewed the literature and found 15 cases with symptoms referable to the urologic system. Of these 15, the correct antemortem diagnosis was made in 9, indicating that a history of radiation of pain to the flanks seems to facilitate the diagnosis.

Radiation of pain to the extremities does not occur with as great frequency as might be expected. In 8 instances the pain was noted to radiate down either the upper or lower limbs.

*Recurrent Pain.* Of the 45 patients with initial pain as the presenting symptom, recur-

rent pain occurred in 29. This pain was described variously as a dull ache resembling the initial pain but less severe, an intermittent aching, a pleuritic pain, a tearing pain, or a sharp, needle-like pain.

Recurrent pain was present in the chest in 9 patients, and in several of these it had a pleuritic character, being aggravated by respiration. Of the 11 patients having recurrent pain in the abdomen the discomfort was most frequently described as a full aching pain. In the remaining patients the pain centered in the back in 4, in the flanks in 3, in the shoulders in one, and in the legs in one.

Recurrence of pain was, therefore, quite common, and indicated either progressive dissection or ischemia resulting from interruption of the blood supply to such locations as the intestinal tract, kidneys, spinal cord, or extremities.

*Onset of Syncope.* A history of an attack of syncope with recovery of consciousness and no history of pain occurred in only one patient. In another patient a syncopal attack occurred initially, but this was subsequently followed by epigastric pain. In 3 additional patients, syncope occurred, but it was preceded by chest pain in 2 of these, and neck pain in the third. The occurrence of syncope in association with dissecting aneurysm was stressed by Hamburger and Ferris,[28] who described 6 patients in whom the outstanding symptom at the onset was syncope or weakness. Four of their 6 patients fainted at the onset or shortly thereafter, and the other 2 suffered from dizziness and weakness, but did not lose consciousness. They point out the fact that syncope is uncommon in association with myocardial infarction, but not with dissecting aneurysm. The suggestion was offered that the syncope was due to involvement of the depressor nerve endings in the aortic arch. The more likely explanation is cerebral ischemia either resulting from the pooling of large quantities of blood in the false passage, or due to blockage or dissection of the innominate and common carotid arteries.

Six patients, 2 of whom had hemiplegia, were admitted to the hospital while unconscious, with no antecedent history of pain. The dissection in these patients had involved one or more of the major blood vessels to the brain.

*Other Symptoms.* In addition to the major presenting symptomatology which has just been discussed, a tabulation of secondary symptoms may be found in table 4. Dyspnea predominated, being recorded in 25 patients. Next in frequency was vomiting, found in 12 patients. In 8 of these with vomiting the dissection had extended down into the abdominal aorta. Oliguria was reported in 5, and in 4 of these the renal arteries were involved in the dissection. In the 3 patients with hemoptysis, necropsy disclosed dissection along the pulmonary arteries and into the roots of both lungs. Melena occurred in 2 patients, in one of whom the dissection had involved the superior mesenteric artery. The clinical-pathologic correlation of these symptoms has been described so that their occurrence can be properly evaluated and interpreted.

TABLE 4.—*Secondary Symptoms*

| Symptom | No. of Patients |
|---|---|
| Dyspnea | 25 |
| Vomiting | 12 |
| Nausea | 6 |
| Orthopnea | 6 |
| Oliguria | 5 |
| Hemoptysis | 3 |
| Ankle edema | 2 |
| Melena | 2 |
| Hematemesis | 2 |
| Hematuria | 2 |

## CLINICAL FINDINGS

*General Appearance of the Patient.* The patient was usually in acute distress, writhing and tossing about, complaining bitterly of excruciating pain in his chest or abdomen. The pain was often so intense as to cause him to double up or lie on the floor in an attempt to obtain relief. He frequently presented the picture of shock, with pallor, perspiration, and cold, clammy extremities.

*Pulse Rate and Respiration.* In the majority of cases, the pulse rate at the time of the dissection was recorded as ranging between 80 to 100 per minute. The highest rate was 120 per minute, and this was found in 4 patients. In 5 instances, a bradycardia was present with

rates of 50 per minute in 3, and 40 per minute in the other 2 subjects. Both patients with rates of 40 per minute were thought to have a complete heart block. At necropsy, in one of these, the dissection had descended into the interauricular septum to approach the region of the A-V node. Similar findings were not present in the second case. Davis[66] described a patient in whom the dissection had descended inferiorly into the interventricular septum, and finally ruptured into the right ventricle.

In 4 of the "chronic" cases, cardiac arrhythmias were present. These consisted of complete heart block, auricular fibrillation in 2 cases, and a ventricular tachycardia complicating a recent posterior myocardial infarction.

TABLE 5.—*Previous History of Hypertension, and Presence of Hypertension, Normal Blood Pressure, and Shock on Admission*

| | Hypertension on Admission | Systolic Hypertension on Admission | Normal B. P. on Admission | Shock on Admission |
|---|---|---|---|---|
| Previous History of Hypertension (34 cases) | 23 | 2 | 2 | 7 |
| No Previous History of Hypertension (24 cases) | 10 | 3 | 5 | 6 |
| Total | 33 | 5 | 7 | 13 |

The absence of arrhythmias in the acute cases is worthy of attention. There were none, except in the two instances of suspected complete heart block described above, and in an additional case in a patient with auricular premature contractions. In the 17 cases reported by David, McPeak, Vivas-Salas, and White,[1] the maximum pulse rate was also 120, and likewise there were no cardiac arrhythmias.

The changes in the respiratory rate are worthy only of brief mention. An increase in the respiratory rate at the onset was universal except in those patients who had been given large doses of morphine. The sudden development of dyspnea after the onset was usually caused by external rupture associated with bleeding into the pleural cavity or mediastinum, or by dissection of the pulmonary artery.

*Temperature.* Of 43 patients admitted during or shortly after the onset of dissection, an elevated temperature varying from 99 to 103 F. was present in 20 instances. Thirteen patients were admitted in shock with subnormal blood pressures, and in all of these the temperature was normal or subnormal. There were 10 others who appeared to be in shock despite elevated blood pressures. Members of this latter group had pallor, perspiration, cold and clammy extremities, and similar symptoms, and their temperatures were either normal or subnormal.

All patients in the hospital who survived forty-eight or more hours were noted to have a febrile course with their temperatures fluctuating irregularly from 99 to 102 F. In those patients who went into shock after admission the temperature became subnormal.

Finally, in the absence of shock, fever was common during the acute and subacute stages of dissecting aneurysm.

*Observations on Blood Pressure.* It is well established that antecedent hypertension is a major factor in the evolution of a dissecting aneurysm. David, McPeak, Vivas-Salas, and White[1] were able to establish a previous history of hypertension in each of their 17 patients. Such was not the case in the present series of patients, composed of persons of the low-income group seen in a large general hospital. Because of the absence of a previous history in many of them, and the not infrequent finding of a normal or subnormal blood pressure on admission, the findings were carefully reviewed (table 5). Values above 140 mm. of mercury systolic and 90 mm. of mercury diastolic were considered abnormal.

A previous history of hypertension (abnormal elevation of both systolic and diastolic) was present in 34 patients (58 per cent), and absent in 24 (42 per cent). In most of these the hypertension was noted to have been of long standing.

Hypertension on admission was present in 23 of the 34 patients with a previous history, and in 10 of the 24 with no antecedent history. The total, therefore, of patients with elevated blood pressures on admission was 33 (56 per cent) of the entire group of 58.

There were 5 patients with systolic hypertension only on admission, and 7 with normal

blood pressures. The group admitted in shock, with subnormal blood pressure, consisted of 13 patients (22 per cent of total). In addition, there were, as previously stated, many patients who clinically appeared to be in shock, in whom the blood pressure was found to be abnormally elevated, having frequently fallen from an even higher original pressure. We have followed the conventional pattern of shock and listed only those patients having subnormal blood pressures in addition to the clinical pattern of shock. The subnormal pressures in some instances is attributed to severe blood loss, and in others, to cardiac tamponade resulting from hemopericardium.

Persistence of hypertension in these patients has been thought by some to be of diagnostic value in the differentiation between dissecting aneurysm and coronary occlusion, in that the blood pressure would be more apt to drop in the latter condition than in the former. Actually, those patients with hypertension who develop a myocardial infarction do have a drop in blood pressure, but the blood pressure may remain above the normal range. Nine of the patients with elevated blood pressures on admission showed a significant drop in pressure during their hospitalization. Two of this group developed aortic diastolic murmurs and their blood pressures fell from 210/120 to 132/72, and from 190/110 to 140/75 respectively. Careful observation should disclose that this type of change occurs frequently, and when it does its diagnostic inference is far more important than that of the maintenance of an elevated pressure. The remaining 7 patients developed shock with marked reduction in their blood pressures some time after admission. Actually, there were 34 (53 per cent) of the patients in whom shock, normal blood pressure, and systolic hypertension were present on admission, or whose blood pressure following admission was not sustained at the admission level.

The 11 patients without previous history of hypertension, who were admitted in shock or with normal blood pressures, all had left ventricular hypertrophy post mortem in the absence of valvular disease. The left ventricular wall measured 14 to 21 mm. in these subjects. Because of this, it was felt that pre-existing hypertension has been established either directly or indirectly in all of the cases reviewed.

*Pleural Effusion.* Pleural fluid was detected on physical examination in 6 patients; in 4 it was in the left side of the chest, and in the remaining 2 it was bilateral in one and on the right in the other. The increased incidence of left-sided hemothorax over hemothorax of the right side in dissecting aneurysms is well known. Hemorrhage into the left pleural cavity at postmortem examination was present in 11 of the 58 subjects (19 per cent). In 2 of these there was an accompanying hemopericardium. Rupture into the right pleural cavity was present at autopsy in 2 instances. The increased incidence of hemorrhage into the left pleural cavity as contrasted to the right can be explained by the close proximity of the aorta to the left pleural cavity, and by the fact that when dissection of the pulmonary artery occurs it apparently follows the line of least resistance along the left main branch and into the hilum of the left lung.

*Cardiac Enlargement.* Initial physical examination detected cardiac enlargement as being present in 38 of the 58 patients. In 5 additional patients, fluid in the left side of the chest interfered with accurate estimation of the heart size. At autopsy there were only ten hearts weighing less than 400 grams. In each of these cases there was either a history of hypertension or hypertension had been present on admission. Twenty-two per cent of the hearts weighed between 400 and 500 grams, and 55 per cent of the hearts were heavier than 500 grams. There were only 2 subjects in whom the left ventricle measured less than 14 mm. in thickness.

*Cardiac Tamponade.* Hemorrhage into the pericardium was suspected in only one patient prior to death. At autopsy it was found in 20 of the 58 subjects (34 per cent). The pericardium proved to be the commonest site of rupture.

*Pericardial Friction Rub.* A to-and-fro pericardial friction rub was detected in 3 patients. This finding in association with a dissecting aneurysm may be due to slow seepage of blood into the pericardial sac through an adventitial perforation, to a uremic pericarditis from dis-

section of the renal arteries and the resultant uremia, or, finally, to a pericarditis accompanying myocardial infarction which has resulted from involvement of the coronary arteries by dissection. If the friction rub is due to seepage of blood through an adventitial perforation it is a particularly ominous sign in regard to the immediate prognosis, and should be looked upon as a herald of incipient cardiac tamponade.

*Cardiac Murmurs.* Resnik and Keefer,[29] in 1925, reported the presence of aortic insufficiency in a 57 year old Negro with negative serologic reactions, who at postmortem examination was found to have a dissecting aneurysm of the aorta with no discernible valvular

TABLE 6.—*Distribution of Cardiac Murmurs in Fifty-Eight Patients With Dissecting Aneurysm of the Aorta*

| Type of Murmur | Incidence |
|---|---|
| Aortic diastolic (alone) | 5 |
| Aortic diastolic and aortic systolic | 8 |
| Aortic diastolic and systolic, and mitral systolic | 3 |
| Aortic systolic (alone) | 3 |
| Aortic systolic and mitral systolic | 3 |
| Mitral systolic and mitral diastolic | 1 |
| Mitral systolic (alone) | 9 |
| Total | 32 |

pathologic process. The explanation of the peripheral signs of aortic insufficiency was that the drop in blood pressure was due to the leakage of blood from the main channel into the aneurysmal sac, resulting in a high pulse pressure similar to that of a peripheral arteriovenous aneurysm. The diastolic murmur was attributed to the same mechanism since the intimal opening lay just above the aortic valve. In 1933, Hamman[30] described a similar case in which the diagnosis of dissecting aneurysm of the aorta had been made antemortem. In this case, the aneurysmal sac was too small to permit the shunting of blood suggested by Resnik and Keefer. Hamman felt that the aortic regurgitation was most likely due to the valvular incompetency resulting from stretching or dilatation of the aortic ring.

There are numerous case reports[31–37] of patients admitted with the findings of aortic insufficiency and aneurysmal dilatation of the ascending aorta, in whom, despite negative serologic reactions, the diagnosis of syphilitic heart disease was made. At autopsy a dissecting aneurysm was found and the aortic valve appeared normal. Gouley and Anderson,[36] in 1940, reported 6 chronic "healed" dissecting aneurysms of the aorta, all associated with aortic diastolic murmurs with peripheral signs of aortic insufficiency. Five out of the 6 patients had negative serologic reactions. The antemortem diagnosis in each case had been that of syphilitic heart disease. The presence of negative serologic reactions is important as approximately 90 per cent of patients with syphilitic aortitis have positive serologic reactions.[38] Consequently, an aortic diastolic murmur accompanied by aneurysmal dilatation of the ascending aorta and negative serologic reactions should make the clinician consider the diagnosis of a dissecting aneurysm.

*Incidence of Aortic Diastolic Murmurs in Fifty-Eight Cases of Dissecting Aneurysm of the Aorta Proved at Autopsy.* In table 6 there is tabulated the incidence of cardiac murmurs found in 32 of the 58 patients. Aortic diastolic murmurs were present in 16 patients (27.5 per cent of the total). In 2 instances the diastolic murmurs had a musical quality. In 4 subjects the heart tones were inaudible because of cardiac tamponade, so that the incidence of aortic insufficiency could have been higher. David, McPeak, Vivas-Salas, and White[1] found basal diastolic murmurs in 9 of 17 patients (56 per cent). They felt that this incidence was higher than that expected among hypertensive patients, but that any attempt to correlate the incidence of aortic dissection on such data might prove misleading. Flaxman[17] found aortic diastolic murmurs in 10 of 19 persons with dissecting aneurysm at the Cook County Hospital. Recently Baer and Goldburgh[39] reported 44 patients, 6 of whom had aortic diastolic murmurs.

One hundred consecutive autopsy cases of hypertensive heart disease were reviewed to determine the incidence of aortic diastolic murmurs accompanying hypertension in the ab-

sence of aortic valve disease. Aortic diastolic murmurs were present in 2 cases (2 per cent). Garvin[40] reviewed 200 consecutive cases of hypertension and found aortic diastolic murmurs in 7 per cent.

The total number of mitral systolic murmurs in the present series was 16, exactly equal to the incidence of aortic diastolic murmurs (table 4). This certainly is not the usual finding in hypertension.

Five of the 16 instances of aortic diastolic murmurs were found in a group of 15 patients with chronic or "healed" dissecting aneurysms. The remaining 11 were distributed among 43 individuals with acute dissections. In several of the patients among the acute cases the aortic diastolic murmur was not present upon admission, but appeared during progressive dissection after hospitalization.

loosened, and the corresponding cusp dropped to a lower level in the aortic ring. Another proposed explanation was that the dissection extended inferiorly into the aortic ring and that the resultant hematoma distorted the valve ring, or displaced one of the cusps inferiorly, and resulted in valvular incompetency. One of our patients was found at necropsy to have the right cusp displaced inferiorly by a hematoma which had dissected down into the aortic ring.

In the 16 patients with aortic insufficiency the dissection had descended down into the aortic ring in 10. In 4 others it had extended proximally to within 1, 2, 3, and 5 cm. of the aortic ring. In the remaining 2 patients, the dissection had extended proximally in the arch of the aorta to the level of the left subclavian artery.

TABLE 7.—*Measurements of Aortic and Pulmonic Valves*

| 54 Cases of Dissecting Aneurysm of the Aorta | No. of Cases | % | 100 Cases of Hypertension Without Dissection | No. of Cases | % |
|---|---|---|---|---|---|
| Group I: Pulmonic valve 0.5 to 2.0 cm. greater than aortic valve | 20 | 37 | Group I: Pulmonic valve 0.5 to 1.5 cm. greater than aortic valve | 38 | 38 |
| Group II. Aortic and pulmonic valves equal | 13 | 24.2 | Group II: Aortic and pulmonic valves equal | 20 | 20 |
| Group III: Aortic valve 0.5 to 4.2 cm. greater than pulmonic | 21 | 38.8 | Group III: Aortic valve 0.5 to 1.5 cm. greater than pulmonic | 42 | 42 |

*Explanations of the Mechanism of the Development of Aortic Insufficiency in Dissecting Aneurysms of the Aorta.* Numerous explanations have been offered for the mechanism of the appearance of aortic insufficiency in association with dissecting aneurysms. Two of these have already been discussed. The first was that of Resnik and Keefer,[29] who felt that the false sac functioned similarly to an arteriovenous shunt, and that regurgitation through the intimal tear above the aortic valves produced a diastolic murmur. The second was that of Hamman and Apperly,[30] who felt that stretching of the aortic ring resulted in incompetency. Peery[41] reported 6 cases of intimal tears without dissection localized in the proximal portion of the ascending aorta. He stated that if the intimal tear was at or just above an aortic commissure and transverse to the commissure, aortic insufficiency resulted. His explanation was that, owing to the gaping of the tear, the commissure

Minimal pathologic changes of the aortic valve were found in 3 of the 16 patients with aortic insufficiency. In one patient the edges of the valve were thickened and rolled, with fusion between the right and posterior cusps. Two other patients had slight fusion of the edges of the aortic valve leaflets which were not sufficient to result in valvular incompetency.

Measurements of the aortic and pulmonary valve rings were recorded in 54 of the 58 patients. These were compared with similar measurements in 100 individuals with hypertensive heart disease without dissection. This was done to determine whether or not cystic medial necrosis found in the aortas of patients with dissecting aneurysms resulted in greater stretching of the aortic ring than in that due to hypertension not associated with medial necrosis. It was found (table 7) that there was no marked difference in these measurements

in the two groups of patients. Actually, the incidence of aortic valve ring measurements exceeding that of the pulmonic valve ring was 38.8 per cent in the patients with dissecting aneurysms, and 42 per cent in the hypertensive subjects. (Normally, the pulmonic valve ring measurement exceeds the aortic by about 1 centimeter.)

An analysis was also made of the valve ring measurements of the 16 patients with dissecting aneurysm associated with aortic insufficiency (table 8). Here it was found that in only 2 patients in whom the aortic valve exceeded the pulmonic valve by 3.5 and 4.2 cm., could stretching of the valve ring be inferred as being the mechanism for the production of aortic insufficiency.

TABLE 8.—*Valve Measurements in Sixteen Patients With Dissecting Aneurysm With Aortic Insufficiency*

| Measurements | No. of Cases |
|---|---|
| Group I: Pulmonic valve 0.5 to 2.0 cm. greater than aortic valve | 6 |
| Group II: Aortic and pulmonic valves equal | 2 |
| Group III: Aortic valve 0.5 to 4.2 cm. greater than pulmonic valve. Of this group in only 2 patients did the aortic exceed the pulmonic by more than 2 cm. (3.5 and 4.2 cm.) | 8 |

*Significance of Aortic Diastolic Murmurs in Dissecting Aneurysm.* The sudden appearance of a basal aortic diastolic murmur in a patient with hypertension complaining of severe chest or abdominal pain is almost pathognomonic of a dissecting aneurysm of the aorta. To be considered in the differential diagnosis of the sudden appearance of an aortic insufficiency is rupture of an aortic valve cusp. The pain and shock of a dissecting aneurysm are usually absent in association with a ruptured cusp. A drop in the diastolic pressure occurs in both conditions. Ruptured cusps are usually accompanied by a tachycardia, whereas in dissecting aneurysms the pulse rate tends to be normal or that of a bradycardia. Finally, but of extreme importance, is the fact that when an aortic cusp ruptures the valve usually has been damaged by prior disease such as syphilis, arteriosclerosis, rheumatic valvulitis, or bacterial endocarditis.

*Pulsating Masses.* Abnormal pulsating masses in the neck were present in 3 patients, and in the abdomen of one. Correlation with postmortem findings showed that those in the neck were due to dissection of the common carotid artery, and that the one in the abdomen was due to dissection of the abdominal aorta.

*Tenderness of Blood Vessels Involved by Dissection.* Dissection of peripheral arteries is often accompanied by localized tenderness over the involved vessel. This was only observed in 2 cases, and both represented dissection of the common carotid arteries.

*Pulsations in the Major Peripheral Arteries.* Diminished or absent peripheral arterial pulsation in association with dissecting aneurysm of the aorta is caused by the vessel being involved in the dissection so that the false sac becomes distended with blood and partially or completely occludes the lumen, or, in addition, thrombosis may occur within the true lumen. Dissection of the major vessels of the aortic arch results in diminished or absent pulsations of those arteries going to the head or upper extremities, such as the carotid, brachial, or radial. When the dissection has extended inferiorly into the common iliacs it may cause diminished or absent pulsations in such vessels as the femorals, popliteals, and dorsalis pedis.

Eleven patients (19 per cent) were found to have unequal or absent pulsations of major peripheral arteries. This was accompanied by comparable significant differences in blood pressure in the involved extremities in all instances (table 9). The carotid, brachial, or radial artery as the site of unequal or absent pulsations in 5 instances, and the femorals in the remaining 6. These clinical observations were correlated with the postmortem findings, and, except for 2 instances where the findings were inadequately described, the vessels involved by dissection corresponded to those in which the abnormal pulsations had been detected.

In addition to the decreased or absent pulse, the involved extremity was not infrequently found to be cold and pale, with impairment of motor power and diminished sensory perception. These changes, when present, were tem-

porary, and lasted from minutes to hours, depending upon establishment of collateral circulation or re-entry of the false sac into the true lumen by intimal rupture. The inequality of pulse and blood pressure usually persisted despite the disappearance of the other signs of arterial occlusion.

The presence of significant differences in pulse or blood pressure in either upper or lower extremities should render the diagnosis obvious in suspected cases. Of course, an arterial embolus could be responsible for these differences.

Nissim[43] recently reported a new sign in dissecting aneurysm found in a major peripheral vessel which had undergone dissection. This consisted of a reduplication of the pulse in the involved vessel, with a single pulse on the uninvolved side. The reduplication was thought to be attributable to the difference in the rate of flow in the true and false sacs.

*Neurologic Manifestations.* The neurologic disturbances encountered in persons with dissecting aneurysm of the aorta have not received proper emphasis in the literature. The recognition of such changes is of importance if only for the fact that when they are present in suspected cases the incidence of correct diagnosis is greatly increased. Weisman and Adams[44] reported 38 patients with dissecting aneurysm seen at the Boston City Hospital over a ten-year period. These investigators found neurologic symptoms resulting from the dissection in 30 per cent of these patients, and in the patients with such symptoms the correct diagnosis was made in 80 per cent. This was about twice the incidence of correct diagnosis in the patients without neurologic manifestations.

TABLE 9.—*Diminished or Absent Pulsations in Major Peripheral Arteries*

| Vessels and Findings | B. P. | Postmortem Findings |
|---|---|---|
| 1. Left c. carotid—diminished pulsation | R.A. 185/130<br>L.A. 150/130 | Dissection of vessels of aortic arch not described |
| 2. Right c. carotid and right radial—diminished pulsation | R.A. 140/100<br>L.A. 180/100 | Innominate artery involved in the dissection |
| 3. Right radial and right brachial—absent pulsation | R.A. 0/0<br>L.A. 104/80 | Innominate artery, and right subclavian artery involved in dissection |
| 4. Both right and left radials and brachials—absent pulsations | R.A. 0/0<br>L.A. 0/0 | Dissection of vessels of aortic arch not described |
| 5. Right radial—diminished pulsation | R.A. 60/20<br>L.A. 175/125 | Innominate artery involved in the dissection |
| 6. Right femoral—diminished pulsation | R.L. 185/140<br>L.L. 270/145 | Common iliacs dissected |
| 7. Right femoral—diminished pulsation | R.L. 195/140<br>L.L. 225/140 | Common iliacs dissected |
| 8. Right femoral—diminished pulsation | No record | Common iliacs dissected |
| 9. Left femoral—absent pulsation | R.L. 290/140<br>L.L. 0/0 | Common iliacs dissected |
| 10. Left femoral—absent pulsation | R.L. 190/140<br>L.L. 0/0 | Common iliacs dissected |
| 11. Both femorals—absent pulsation | R.L. 0/0<br>L.L. 0/0 | Common iliacs dissected |

R.A. = right arm; L.A. = left arm; R.L. = right leg; L.L. = left leg.

Differentiation between it and dissecting aneurysm is not always easy, but because of the therapeutic implications (use of heparin, dicumarol, and allied drugs) its importance is apparent.

Ellis[12] described the presence of a pulsus paradoxus in a patient with dissecting aneurysm associated with hemopericardium. Its occurrence in conjunction with acute or chronic constrictive pericarditis is well known, and it should most certainly be anticipated in patients with dissecting aneurysm in whom hemopericardium occurs so frequently.

Depending upon the locale of vascular interference, the resultant symptomatology may be found to fall into one of the following three groups: (1) Blockage of the iliac or axillary arteries may result in an ischemic necrosis of the peripheral nerves. The examiner is confronted with a pulseless, cold, weak extremity, with anesthesia and loss of tendon reflexes. These changes are often temporary, lasting from minutes to hours, followed by reappearance of the pulse and return of motor power and other functions, usually due to re-entry of the dissection into the lumen of the involved vessel. (2) Impairment of blood flow through the intercostal arteries is said to cause an ischemic necrosis of the spinal cord. Clinically, there is a flaccid paralysis, urinary retention, and loss of sensation below the involved level. Unfortunately, there is a paucity of pathologic studies of this mechanism. It is known that there is an abundant collateral circulation to the spinal cord; this is so ample that it appears improbable that interference with the lumbar and intercostal arteries alone would result in ischemic necrosis unless the flow through the spinal arteries was simultaneously impaired. (3) Finally, obstruction to the carotids or the innominate artery will result in cerebral ischemia. The clinical picture is variable and may be that of dizziness, confusion, stupor, syncope, hemiplegia, coma, convulsions, blindness, and the like.

Bowman and his collaborators[45] stressed the diagnostic import of "wandering paralysis and vacillating sensory disturbances" occurring below the level of the umbilicus. These were attributed to spinal cord ischemia resulting from interruption of the lumbar and intercostal arteries.

Nine of the 58 patients of this report had definite neurologic symptomatology. Two of these had a left-sided hemiplegia with dissection of the right common carotid artery, found at necropsy. In 5 instances there was a transient weakness of one or both legs, accompanied by numbness and loss of sensation. The dissection was found to have extended down into the iliacs in each of the subjects. One patient had a flaccid paralysis of his right upper extremity due to dissection of the corresponding subclavian artery. Finally, one patient with a flaccid paralysis of both lower extremities and loss of reflexes and sensation was observed. Gross examination of the spinal cord seemed to reveal interruption of its vascular supply, but microscopic examination failed to reveal any pathologic changes. Both common iliacs had also been involved by dissection in this case.

In 5 of these 9 patients (55 per cent) with neurologic symptoms a correct diagnosis of dissecting aneurysm was made, corroborating the findings of Weisman and Adams, who found that the presence of neurologic changes tended to facilitate the correct diagnosis.

### Electrocardiogram in Dissecting Aneurysm of the Aorta

The most difficult problem in the diagnosis of dissecting aneurysm of the aorta has been the differentiation between it and coronary occlusion. Of the 58 autopsied cases of dissecting aneurysm, 20 (34.5 per cent) were incorrectly diagnosed as coronary occlusion. This difficulty was first stressed in 1934 by White, Badger, and Castleman,[16] who described a case of dissecting aneurysm in which the antemortem diagnosis had been that of a coronary occlusion despite an electrocardiogram showing no abnormality. Recently David, McPeak, Vivas-Salas, and White[1] reported that none of the patterns of the electrocardiograms of 17 patients with dissecting aneurysm could be considered normal. Patterns of left ventricular strain or of changes suggesting coronary disease were found to predominate, but none of the patterns were described. The pattern of acute myocardial infarction was not found in any of their cases, and they felt that the absence of this pattern should lend support to the diagnosis of dissecting aneurysm in equivocal cases. Hargrove,[47] discussing this problem, made the statement that in equivocal cases, an electrocardiogram demonstrating no abnormality favored dissecting aneurysm and that one showing abnormality did not rule it out.

Electrocardiograms were made in 40 of the 58 autopsied cases, and have been correlated with the pertinent clinical and pathologic findings (table 10).

TABLE 10.—*Electrocardiograms in Forty Patients With Dissecting Aneurysm of the Aorta*

| Case No. | Electrocardiograph Findings and Interpretation | Clinical and Postmortem Data |
|---|---|---|
| | *Group I: Patterns of myocardial infarction, acute coronary insufficiency, etc.* | |
| 1. | RS-$T_1$, RS-$T_2$, and RS-$T_3$ depressed. Impression: abnormal electrocardiogram | B. P. 90/50. Post mortem: coronary sclerosis, old anteroseptal infarct, and left ventricular hypertrophy |
| 2. | 5/13/44: $T_1$ inverted; RS-$T_2$ and RS-$T_3$ sagging. 5/14/44: $T_1$ now upright; $T_2$ diphasic; RS-$T_2$ and RS-$T_3$ depressed. Impression: acute coronary insufficiency | B. P. 200/140, yet clinical findings of shock present |
| 3. | RS-$T_2$ and RS-$T_3$ depressed. Impression: abnormal electrocardiogram | B. P. 290/100, yet clinical findings of shock present |
| 4. | RS-$T_1$ depressed. Small $Q_3$; RS-$T_2$ and RS-$T_3$ elevated. Impression: abnormal electrocardiogram | B. P. 70/50 (in shock). Post mortem: coronary sclerosis and left ventricular hypertrophy |
| 5. | 3/12/41: Low-voltage, flat T waves in Leads I, II, III. 3/14/41: $Q_2$, deep $Q_3$; RS-$T_2$ and RS-$T_3$ elevated. Impression: recent posterior myocardial infarction | B. P. 110/60 (in shock). Post mortem: right coronary artery stenotic, with no evidence of occlusion. Left ventricular hypertrophy present |
| 6. | $T_1$ diphasic; $T_2$ and $T_3$ flattened. Impression: abnormal electrocardiogram | B. P. 100/80 (in shock). Post mortem: the dissection had extended down into the interauricular septum and subendocardially into both ventricles |
| 7. | $T_1$, $T_2$, and $T_3$ flattened. Impression: abnormal electrocardiogram | B. P. 190/128 (clinical findings of shock). Post mortem: left ventricular hypertrophy |
| 8. | $T_1$, $T_2$, and $T_3$ low; low voltage. Impression: abnormal electrocardiogram | B. P. 70/50 (in shock). Post mortem: left ventricular hypertrophy |
| 9. | 4/29/44: Left ventricular hypertrophy. 5/6/44: Recent posterior myocardial infarct | B. P. 150/100 (clinical findings of shock). Later B. P. rose to 210/110. Post mortem: coronary sclerosis and recent and old myocardial infarcts |
| 10. | 3/7/43: Acute posterior myocardial infarct; pericarditis. 7/26/43: Impression: old posterior myocardial infarct | Post mortem 7/27/43: healed dissecting aneurysm which had compressed orifice of the right coronary. Old posterior infarct. Left ventricular hypertrophy |
| 11. | 9/14/43: $T_2$ and $T_3$ inverted; RS-$T_1$ depressed; RS-$T_2$ and RS-$T_3$ elevated; $Q_2$ and $Q_3$ present. 12/10/43: RS-$T_2$ and RS-$T_3$ more elevated. Impression: old posterior infarct with recent acute insufficiency | In shock at time of final ECG. Post mortem: the dissection involved the pulmonary artery and extended into the roots of both lungs. Left ventricular hypertrophy |
| | *Group II: Acute pericarditis* | |
| 12. | RS-$T_1$ and RS-$T_2$ elevated; RS-$T_3$ iso-electric; $T_1$ flat; $T_2$ and $T_3$ inverted. Impression: acute pericarditis | Post mortem: fibrinous pericarditis with recent hemopericardium. Left ventricular hypertrophy |
| 13. | 1936: RS-$T_1$, RS-$T_2$, and RS-$T_3$ elevated. Impression: acute pericarditis. 1941: Left ventricular hypertrophy | 1936: Time of original dissection. 1941: Post mortem: healed dissecting aneurysm. Pericardium normal |
| 14. | RS-$T_1$, RS-$T_2$, and RS-$T_3$ elevated. Impression: acute pericarditis | Post mortem: fibrinous pericarditis with recent hemopericardium |

TABLE 10.—*Concluded*

| Case No. | Electrocardiograph Findings and Interpretation | Clinical and Postmortem Data |
|---|---|---|
| | *Group III: Uremia* | |
| 15. | $T_1$ and $T_2$ diphasic; $T_3$ flat. Q-T interval 0.44 second. Impression: uremia, pericarditis | N.P.N. 74 mg.%. Post mortem: malignant nephrosclerosis with uremic pericarditis and uremic colitis |
| 16. | RS-$T_1$ sagging. Q-T interval 0.44 second. Impression: uremia, prolonged Q-T interval | N.P.N. 80 mg.%. Post mortem: both renal arteries dissected resulting in thrombosis and renal infarction |
| | *Group IV: Left ventricular hypertrophy (tracings taken at time of dissection)* | |
| 17–28 | (inclusive) Left ventricular hypertrophy. One patient had an old posterior myocardial infarction | Post mortem: left ventricular hypertrophy. Heart weights: 400 to 700 grams |
| | *Group V: Left ventricular hypertrophy (all these tracings made antecedent to dissection, none being made at time of dissection)* | |
| 29–34 | (inclusive) Left ventricular hypertrophy | Post mortem: left ventricular hypertrophy. Heart weights 450 to 850 grams |
| | *Group VI: Miscellaneous—"chronic or healed" dissecting aneurysms* | |
| 35. | Auricular fibrillation | Congestive heart failure. Left ventricular hypertrophy |
| 36. | Prolonged A-V conduction. Right bundle branch block | Left ventricular hypertrophy |
| 37. | Left ventricular hypertrophy. Complete heart block | I-V septum scarred. Left ventricular hypertrophy. Congestive heart failure |
| 38. | Left bundle branch block | Left ventricular hypertrophy |
| 39. | Recent coronary occlusion. Ventricular tachycardia. Left ventricular hypertrophy | Left ventricular hypertrophy; old anterior and posterior infarcts. Congestive heart failure |
| 40. | Left ventricular hypertrophy. Acute posterior myocardial infarction | Coronary occlusion; left circumflex—old; right coronary—recent. Recent and old myocardial infarcts present |

A classification of the various electrocardiographic patterns encountered in persons with dissecting aneurysm has been formulated after a careful study of the present series along with a review of the literature.

*Group I: Electrocardiographic Patterns of Myocardial Infarction and Acute Coronary Insufficiency.*

A. Myocardial Infarction: Infarction may result from dissection of the media of a coronary artery with resulting thrombosis and occlusion, or, the dissection may extend inferiorly in the aortic wall and compress a coronary vessel from without. Wainwright[48] described a patient with serial electrocardiographic changes characteristic of both anterior and posterior myocardial infarction. The dissection in the aorta was noted to have descended inferiorly to involve the wall of the left coronary artery. The resultant aneurysm in the coronary wall

was filled with a thrombus which occluded the vessel by compressing its lumen. Patient 10, whose history and electrocardiographic tracings are presented, was found at autopsy to have had the orifice of the right coronary artery occluded by a hematoma dissecting down into the aortic ring. An acute posterior myocardial infarction resulted. A case with similar associated electrocardiographic tracings has been reported by Bayley and Monte.[49] In Cabot Case 31391[50] at the Massachusetts General Hospital, both coronaries were involved in a like manner, but electrocardiographic changes typical of myocardial infarction were absent.

*Case 10.* The patient, a 28 year old white woman with a known history of hypertension of ten years' duration, entered the Los Angeles County Hospital on March 28, 1943, complaining of the sudden onset of severe, crushing substernal pain, which radiated to her left shoulder and down her left arm. The pain was unrelated to effort and came on about 2:00 A.M. while in bed. It was accompanied by dyspnea, nausea and vomiting.

The patient was in acute distress and complained of severe substernal pain. Her skin was pale, moist, and clammy. Her temperature was 97 F., her pulse rate 110 per minute, and respiration rate 30 per minute. The blood pressure was 210/150. The retinal vessels had a copper-wire appearance; they were tortuous and arteriovenous nicking was present. The lungs were clear. The heart was enlarged on percussion. The point of maximal impulse was in the sixth intercostal space 2 cm. to the left of the midclavicular line. A diastolic murmur was heard over the primary and secondary aortic areas. The remainder of the physical examination revealed no abnormalities.

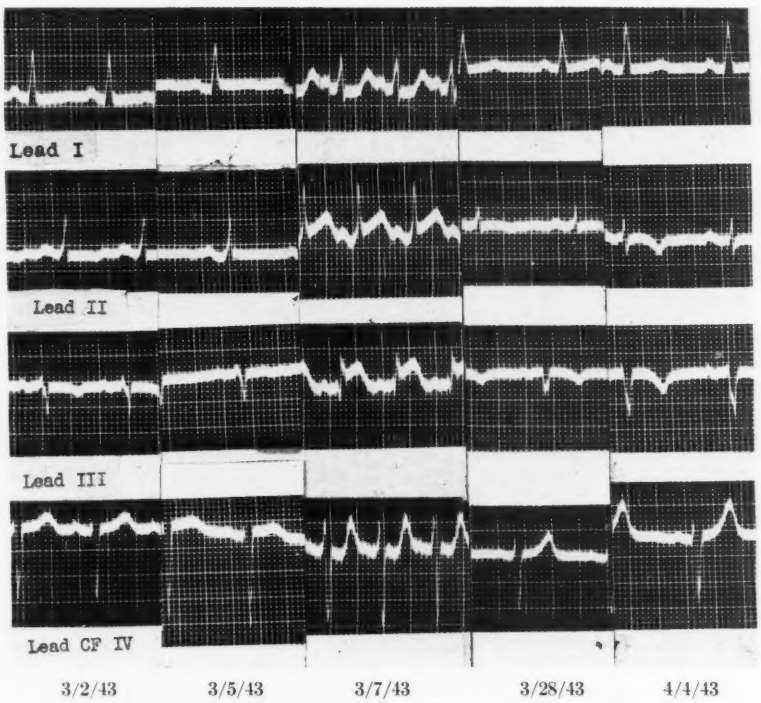


Fig. 1. Electrocardiograms of Patient 10 (see text)

The hemoglobin was 80 per cent. There were 10,200 white blood cells per cu. mm. of blood. The urinalysis showed +3 albumin reaction and 10 to 12 white blood cells per high-powered field. The sedimentation rate was 21 mm. per hour, the nonprotein nitrogen 70 mg. per 100 cc. of blood, and the serologic reaction was negative.

The following electrocardiograms were made (fig. 1): On March 3, 1943, the tracing showed sinus tachycardia, with a heart rate 100 per minute; RS-T segments in Leads I, II, and III depressed; in Lead I the T wave was flat, in Lead II it was diphasic, and in Lead III inverted. The diagnosis of

acute coronary insufficiency was made. On March 5, 1943, the RS-T segments in Leads I and II were elevated; in Lead III they were isoelectric. The diagnosis of possible pericarditis was made. On March 7, 1943, the RS-T segments in Lead I were depressed; in Leads II and III they were elevated; there was a prominent Q wave in Lead III. The diagnosis of acute posterior myocardial infarction was made. On March 28, 1943, the RS-T segment in Lead I was isoelectric, in Lead II depressed; the T waves in Leads II and III were inverted. On April 4, 1943, $T_2$ and $T_3$ were further inverted and coved. The diagnosis of healing posterior myocardial infarct was made.

During the first four weeks of hospitalization the patient's course was febrile with the temperature fluctuating between 100 and 101 F. On her third hospital day she had a convulsion, her blood pressure dropped to 80/0, and she remained stuporous for the ensuing twenty-four hours. An electrocardiogram at this time showed an acute posterior myocardial infarct. Following this, the patient complained of precordial pain for the next three and one-half weeks. A pericardial friction rub was first heard on March 20, 1943. On May 25, 1943, the patient was sent home.

On July 26, 1943, two months after discharge, she was readmitted to the hospital, and complained of severe precordial pain radiating through her chest to her back and up into her neck.

She was dyspneic, orthopneic, pale, cold, and tossing about with pain. She was afebrile. The blood pressure was 185/90. There were a few moist râles at both lung bases. The point of maximal impulse was in the sixth intercostal space 2 cm. outside the midclavicular line. A mitral systolic and an aortic diastolic murmur were present. The findings of the remainder of the physical examination were noncontributory.

The electrocardiogram was that of an old posterior myocardial infarct.

Shortly after admission the patient became pulseless, comatose, and respiration ceased.

On postmortem examination, the pericardial sac was found to be obliterated by adhesions and the visceral pericardium to be distended by a recent subepicardial hemorrhage. The heart weighed 500 grams. The left ventricular wall was hypertrophied and measured 16 millimeters. The aortic and pulmonic valves both measured 7.5 centimeters. The aorta had an old intimal tear 1.5 cm. above the aortic valve which communicated with an aneurysmal sac measuring 3 by 3 by 8 centimeters. On the left anterolateral aspect of the sac there was a recent tear which had ruptured into the adventitia and dissected down into the subepicardial space. This sac distended with blood occluded the ostium of the already narrowed right coronary artery. There was a healed myocardial infarct on the posterior wall of the left ventricle. Microscopic examination of the aorta showed medial necrosis with cyst formation.

Case 5 illustrates myocardial infarction without coronary occlusion. The patient, on admission, was in shock, and the electrocardiogram showed tracings characteristic of a recent posterior myocardial infarct. At autopsy there was no evidence of coronary occlusion, but the right coronary artery was markedly stenotic. Similar cases have been described by Kenny[51] and by Bourne and Mills.[52]

In addition, it is obvious that myocardial infarction may occur independently of the dissection. Electrocardiographic patterns of old myocardial infarction, posterior type, were found in two instances. In one of these (Case 32), coronary thrombosis and myocardial infarction had occurred antecedent to the dissection. In the other (Case 40), a chronic or "healed" dissection, it had occurred subsequent to the dissection. Because of the almost universal coexistence of hypertension in patients with dissecting aneurysms, and the known frequency with which coronary artery disease complicates hypertension, all three may be encountered in the same patient, and the diagnosis is made with difficulty.

B. Acute Coronary Insufficiency, due to Reduction of Coronary Blood Flow because of Shock, Tachycardia, Anemia, "Coronary Spasm": Moderate to severe coronary atherosclerosis present in many of these patients predisposes to the development of this type of pattern, namely, depression of the RS-T segments, with lowering to inversion of the T waves. No previous reports of this pattern in dissecting aneurysm were found in the literature. One reason is that this is a difficult, if not impossible diagnosis to make in the presence of left ventricular hypertrophy. Some feel that the pattern of left ventricular hypertrophy actually reflects left ventricular ischemia. Not infrequently these patients have been receiving digitalis which will also cause RS-T segment shifts and T-wave inversion. Patterns thought typical of acute coronary insufficiency were present in 3 cases (Cases 1, 2, and 3).

C. Acute Ventricular Strain Superimposed upon Old Posterior Myocardial Infarct: One

patient (Patient 11) was of particular interest in that the electrocardiographic pattern was that of acute right ventricular strain superimposed upon the pattern of an old posterior myocardial infarct. At autopsy the dissection was found to involve the pulmonary artery and its branches, extending into the hilar regions of both lungs.

*Group II: Pericarditis.* Weiss[53] discussed the occurrence of pericarditis in association with dissecting aneurysm, and commented upon its infrequency. At least 5 cases were found[54–58] which had been previously reported. All of these patients had pericardial friction rubs and electrocardiographic tracings typical of pericarditis. The mechanisms of the production of pericarditis in dissecting aneurysm are multiple. Most frequently, there is a slow leak of blood into the pericardial sac, and deposition of fibrin upon the lining of the pericardial cavity. This usually heralds an imminent cardiac tamponade. Secondly, a uremic pericarditis may be present, due to either dissection and resultant thrombosis of one or both renal arteries, or primary renal failure of malignant nephrosclerosis, chronic nephritis, and similar conditions. Still another cause would be pericarditis accompanying a myocardial infarction. Patterns of acute pericarditis were present in 4 of the patients in the present series. In one it was thought to be due to a uremic pericarditis. In 2 others (Patients 12 and 14) it was caused by a slow leakage of blood into the pericardial sac. Case 12 has been described in detail with illustrative electrocardiograms. In the remaining case the pericarditis accompanied a myocardial infarction caused by the dissection.

*Case 12.* The patient, a 35 year old Negro garage attendant, was admitted to the Los Angeles County Hospital on February 10, 1941, complaining of severe, crushing, substernal pain which radiated through to the back, and came on while he was engaging in sexual intercourse. The pain was accompanied by dyspnea, nausea, and vomiting. Hypertension had been present since the patient was 12 years of age.

On admission, the patient was heavily sedated with morphine and had obvious respiratory depression. The temperature was 100.2 F., the pulse rate 120 per minute, and respiratory rate 12 per minute. Both pupils were constricted, and reacted poorly to light. The lungs were clear. Cardiac enlargement was present, the point of maximal impulse being in the fifth intercostal space near the anterior axillary line. Gallop rhythm was present. The blood pressure was 185/145 in the right arm, and 180/150 in the left arm. The remainder of the physical examination revealed no abnormality.

The hemoglobin was 60 per cent, and there were 3.7 million red blood cells and 8,200 white blood cells per cu. mm. of blood. The sedimentation rate was 28 mm. per hour. In the phenosulfonphthalein test, the dye appeared in five minutes; 30 per cent was present in the first sample and 10 per cent in the second. The nonprotein nitrogen value was 32 mg. per 100 cc. of blood. The icteric index was 19 units. The Wassermann and Kahn reactions were negative. X-ray examination of the chest showed that the left ventricle was enlarged and that there was marked widening of the ascending aorta.

Several electrocardiograms were made (fig. 2). In the tracings made on January 13, 1941, the RS-T segments in Leads I and II were elevated; in Lead III they were isoelectric. Left axis deviation was manifest. The diagnosis was acute pericarditis. On January 16, 1941, elevation of the RS-T segments in Leads I and II was increased. On January 20, 1941, the RS-T segments in Leads I and II had returned to the base line; $T_2$ was flat and $T_3$ inverted. On February 5, 1941, there was evidence of electrical alternans in Leads II and III. The RS-T segments were now isoelectric. $T_1$ was low, $T_2$ and $T_3$ inverted.

During the hospitalization, the patient's temperature fluctuated between 100 and 101 F. Pain in the left side of his chest, aggravated by deep breathing, persisted. A week after admission a pericardial friction rub was detected, and the presence of pericarditis was substantiated by electrocardiograms. Later, a to-and-fro basal murmur appeared, and the diagnosis of a dissecting aneurysm was made. The patient appeared to be improving when he died suddenly on February 19, his ninth hospital day.

At autopsy, 600 cc. of clotted blood were found in the pericardial sac. The epicardium was shaggy, reddish gray in appearance, with tags of both fibrinous exudate and organized fibrous tissue. On the anterior surface of the aorta there was a small tear in the adventitia which is the site of rupture into the pericardial sac. When the aorta was opened, about 1 cm. above the valve, there were noted two transverse intimal tears which communicated with a dissecting aneurysm, which extended distally to the level of the right renal artery. At this point there was another intimal tear which marked the site of re-entry. The false sac was filled with a large antemortem blood clot. The heart weighed 800 grams. The left ventricular wall was 20 mm. in thickness, the right 7 millimeters. The aortic valve measured 5 cm., and the pulmonic 8 centimeters.

The microscopic examination of the aorta showed medial degeneration with cyst formation. The pericardium showed a subacute fibrinous pericarditis.

*Group III: Uremia.* Tracings consistent with uremia were found in 2 instances (Cases 15 and 16). In Patient 15 it was due to primary renal involvement in the form of malignant nephrosclerosis. At autopsy a uremic pericarditis and colitis were also found. In the other patient the uremia resulted from the dissection involving the renal arteries with resultant thrombosis and renal infarction. The electrocardiographic changes characteristic of uremia are prolongation of the Q-T interval, sagging of the RS-T segments, and T-wave flattening and inversion. These changes may be specifically related to the disturbances of calcium and phosphorus or potassium metabolism occurring in conjunction with uremia. The electrocardiographic pattern of uremia occurring in association with dissecting aneurysms of the aorta has not been previously described.

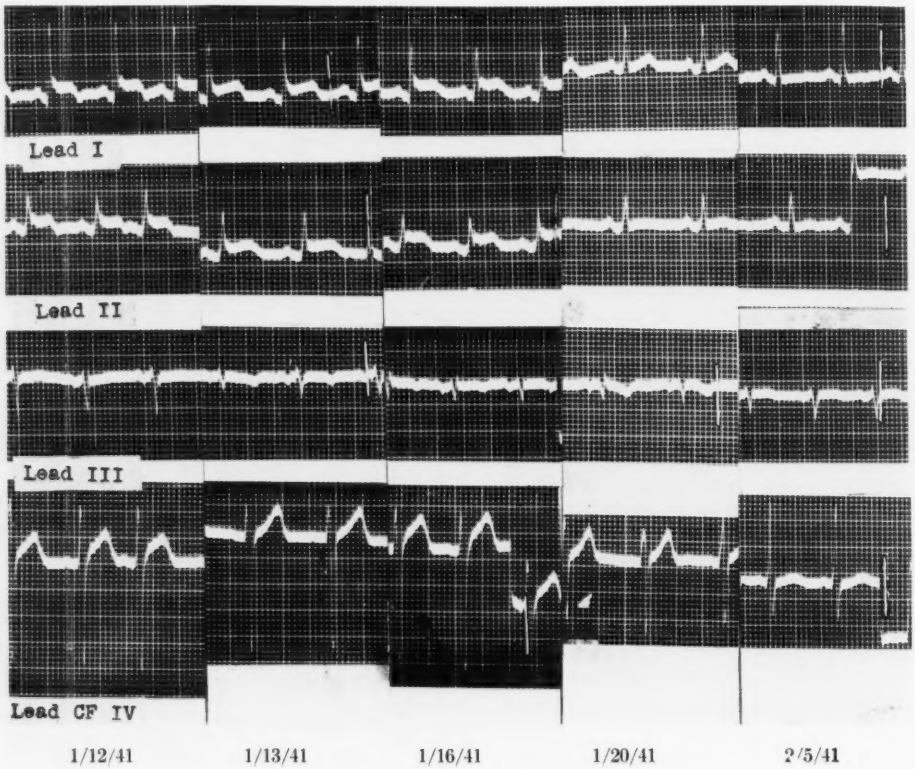


Fig. 2. Electrocardiograms of Patient 12 (see text)

*Case 15.* The patient, a 32 year old Mexican woman, entered the Los Angeles County Hospital on April 1, 1945, complaining of blindness, vomiting, and urinary frequency of two months' duration. At the age of 13 years she had had "kidney trouble." Five years ago, after the birth of her fifth baby, she began to have severe occipital headaches, and hypertension was observed for the first time. Her sixth and seventh pregnancies were complicated by severe headaches and ankle edema. Progressive loss of vision began just prior to the birth of her eighth child (December, 1942).

The patient appeared well nourished and in no acute distress. The temperature was 99 F., the pulse rate 90 per minute, and respiration rate 20 per minute. The blood pressure was 222/180. Light perception was diminished in the right eye, and absent in the left. Examination of the fundi showed narrowed arterioles, arteriovenous nicking, hemor-

rhages, and exudates. The discs were pale. The lungs were clear. The heart was enlarged and the point of maximal impulse was in the fifth intercostal space at the anterior axillary line. The sounds were of fair quality. The remainder of the physical examination revealed no abnormality.

The red blood count was 4.9 million, and the hemoglobin was 92 per cent. There were 15,050 white blood cells per 100 cu. mm. of blood. The urine examination showed a specific gravity fixed between 1.010 and 1.013, +3 albumin reaction, 75 to 100 red blood cells and 30 to 40 white blood cells per high-powered field. The nonprotein nitrogen was 74 mg. per 100 cc. of blood. The Wassermann and Kahn reactions were negative.

The electrocardiogram showed a small $Q_2$ and a prominent $Q_3$. $T_1$ and $T_2$ were diphasic, and $T_3$ was flat. The T wave in $CF_4$ was diphasic. The Q-T interval was 0.44 second (fig. 3). These changes were thought consistent with those due to uremia.

On her third hospital day the patient complained of severe epigastric pain radiating to the precordium. The pain persisted for about a week and was localized in the epigastrium. Her course was progressively downhill, and after three months of hospitalization, she became disoriented and expired on July 6, 1945. The antemortem diagnosis was malignant nephrosclerosis.

On postmortem examination the pericardial sac was found to contain no free fluid. There were recent adhesions between the visceral and parietal pericardium, and a recent fibrinous pericarditis was found over the epicardium. The heart weighed 500 grams. The left ventricle measured 15 mm., the right 3 millimeters. In the aorta there was an intimal tear just distal to the origin of the left subclavian artery. This communicated with a dissecting aneurysm which extended distally to a point midway between the superior and inferior mesenteric arteries. The false sac was filled with two large organized blood clots.

The kidneys were normal in size and their surfaces were covered with numerous petechial hemorrhages. Microscopically, arteriolonecrosis was present accompanied by hemorrhage into the glomeruli and the interstitial tissue. The findings were thought to be typical of malignant nephrosclerosis.

*Group IV: Left Ventricular Hypertrophy.* There were 12 patients in this group whose electrocardiograms were made at the time of the dissection. All these patients were found at autopsy to have left ventricular hypertrophy.

In addition there were 6 patients whose electrocardiograms were made prior to the onset of dissection. In none of these had electrocardiograms been made at the time of the dissection. All of the electrocardiographic patterns were characteristic of left ventricular hypertrophy, the presence of which was corroborated at the postmortem examination.

*Group V: Miscellaneous.* This included the patients with "healed" or chronic cases who re-entered the hospital finally to die of congestive heart failure, coronary artery disease, cerebral hemorrhage, or similar catastrophe. Electrocardiograms in 6 of these patients were chiefly the patterns of left ventricular hypertrophy, bundle branch block, coronary occlusion, or cardiac arrhythmias (such as auricular fibrillation, ventricular tachycardia, and complete heart block with ventricular extrasystoles).

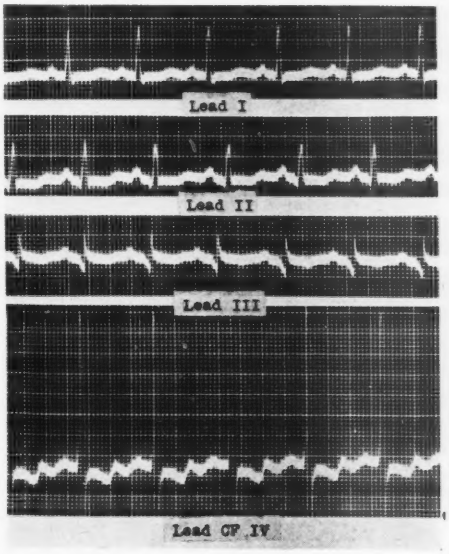


Fig. 3. Electrocardiograms of Patient 15 made on April 2, 1943, showing prolonged Q-T interval (see text).

*Comment on the Electrocardiographic Patterns Found in Association with Dissecting Aneurysm:*

1. Review of the electrocardiograms in 40 patients with dissecting aneurysm revealed them all to be definitely abnormal.

2. The most common pattern was that of left ventricular hypertrophy. This was present in 25 cases (62 per cent).

3. The patterns of myocardial infarction, acute coronary insufficiency, and the like, were found in 13 cases (22.7 per cent).

4. Patterns of acute pericarditis, due to seepage of blood into the pericardial sac, were found in 4 cases (10 per cent).

5. Electrocardiographic patterns of uremia occurred in 2 patients (3.4 per cent), secondary to dissection of the renal arteries, or owing to primary renal disease.

6. Absence of electrocardiographic changes of myocardial infarction should support the diagnosis of dissecting aneurysm in equivocal cases. The presence of such changes does not rule out the possibility of a dissecting aneurysm, as it has been shown that a dissecting aneurysm may result in or be accompanied by a myocardial infarction. There is no specific electrocardiographic pattern in dissecting aneurysm. The patterns may be as varied as the clinical syndromes encountered.

### Roentgenologic Findings

Since the patient in the acute stage of suspected dissecting aneurysm should not be moved and should be spared any unnecessary activity the x-ray study at this time should be limited to a bedside examination. Also the x-ray findings will hardly affect the therapeutic approach. If the initial dissection is survived, thorough roentgen-ray study can be performed at a later date.

Davy and Gates,[59] in 1922, reported the first case of dissecting aneurysm diagnosed antemortem in which the diagnosis had been confirmed by the x-ray findings. The x-ray film was reported as showing a widened and somewhat radiolucent shadow of the aortic arch and descending aorta.

Ritvo and Votta[60] felt that the most significant finding was the presence of a widened supracardiac shadow. If the dissection was localized a circumscribed or saccular deformity of the aorta resulted. If the dissection was diffuse and widespread a generalized widening of the supracardiac shadow was expected. Wood, Pendergrass, and Ostrum[61] felt that the increase in width of the innominate or other large vessels originating from the aortic arch was the most pathognomonic roentgen-ray sign.

X-ray examination of the chest was performed in 20 of the 58 patients of this report. Ten, or 50 per cent of these, showed widening and dilatation of the ascending and transverse portions of the arch of the aorta. In 2 additional patients the widening was limited to the descending thoracic aorta. In 3 of these the findings were reported as being consistent with a dissecting aneurysm, and in 2 more as being consistent with aneurysm.

On fluoroscopic examination the aortic pulsations are usually diminished. However, they may be normal or even increased, depending upon the location and the extent of the dissection. As in other aneurysms, the esophagus and trachea may be displaced.

A most significant finding is the sudden appearance of an increase in the width of the aorta, in the region of the arch or in its descending portion. Roesler, Gifford, and Betts[62] reported a case in which this was detected by serial roentgenograms, and thus the correct diagnosis was facilitated.

Golden and Weens[72] reported a dissecting aneurysm involving the arch and descending aorta in which angiocardiography using 70 per cent diodrast demonstrated a double-barrelled contour. The diagnosis of dissecting aneurysm was subsequently confirmed at operation.

Cardiac enlargement, chiefly left ventricular in type, was found in 11 of the 20 patients, and in an additional 4 its presence was obscured by a coexisting left pleural effusion.

If external rupture into the pericardial sac has occurred at the time the x-ray examination of the chest is made the findings will be those of a pericardial effusion. Rupture into the left pleural cavity, almost always left sided, can also be demonstrated by roentgenograms. A left pleural effusion was present in 4 of the present series of cases (20 per cent).

Weiss, Kinney, and Maher[63] described a chronic "healed" dissecting aneurysm in which extensive atherosclerosis developed in the false sac. The roentgenogram of the chest disclosed a double-barrelled aorta with calcification in both the true and false sac. No similar case has been described in the literature.

### Laboratory Findings

*Serologic Studies.* Wassermann and Kahn tests were performed in 48 of the 58 patients. Of these, the reaction was reported positive

in 6 instances. Three of the 6 patients were found at autopsy to have syphilitic aortitis. A fourth patient was inadequately studied in that a microscopic study was not performed, and the diagnosis of syphilitic aortitis was made on gross appearance alone. The gross appearance of medial necrosis is often not unlike that of syphilitic aortitis, so the diagnosis in this case is certainly open to question. The remaining 2 patients with positive reactions had no evidence of syphilitic aortitis.

In addition, there were 2 other patients with negative reactions who had syphilitic aortitis at autopsy, making a total of 5 definite cases of syphilitic aortitis.

The significance of negative serologic reactions in the presence of aortic insufficiency associated with aneurysmal dilatation of the ascending aorta has been discussed under the heading of cardiac murmurs. Of the 16 patients in whom aortic diastolic murmurs were observed the serologic reaction was positive in 2 (12 per cent). At autopsy both of these had syphilitic aortitis, but the aortic valves were uninvolved. This low percentage of positive serologic reactions encountered (in association with diastolic murmurs, and the like) is certainly in sharp contrast to the known 80 to 90 per cent positive reactions in patients with syphilitic aneurysms and coexisting aortic insufficiency. Because of this, it is worthy of re-emphasis that dissecting aneurysm be considered in the diagnosis of those patients with aortic insufficiency, aneurysmal dilatation of the ascending aorta, and negative serologic reactions.

*Blood Count.* Anemia: A normochromic normocytic anemia was often present shortly after the onset of dissection. It was probably caused by acute blood loss from hemorrhage into the mediastinum, pleural cavity, retroperitoneal space, or elsewhere. A progressive drop in the red blood cell count and hemoglobin value was frequently observed in those patients who survived the initial insult and advanced into the "subacute" or "chronic" stages. One patient who survived fifteen days had an initial blood count of 4.5 million red blood cells and hemoglobin value of 10.4 grams. Shortly before death his count had dropped to 3.5 million red blood cells and the hemoglobin value was 8 grams. Another patient with a "chronic or healed" case had a red blood cell count of 5.8 million with 17 grams of hemoglobin initially. Two months after admission there were 3.6 million red blood cells and 10 grams of hemoglobin.

Leukocytosis: Most patients at the onset showed a moderate to a marked leukocytosis with a corresponding increase in the polymorphonuclear leukocytes. The white blood cell count varied between 9,600 and 29,500, and most commonly was about 15,000 with a marked polynucleosis. The elevated white blood cell count probably was caused by hemorrhage into the false sac or one of the serous cavities.

*Urinalysis.* Albuminuria varying from a trace to 4 plus was found in many of the cases.

Hematuria was present in 5 instances on microscopic study; in 3 additional ones the urine had been observed as being grossly bloody. One of these with gross hematuria encountered at autopsy had a necrotizing arteriolitis of the kidney, and the clinical diagnosis had been malignant nephrosclerosis. The other 2 patients with gross hematuria were found to have had dissection of the renal arteries with resultant thrombosis and renal infarction. Two of these patients with only microscopic hematuria were likewise observed to have dissection involving the renal arteries.

In 1945, Blain, Glynn, and Hiratzka[27] reviewed the literature and were only able to find 15 patients with urologic symptoms such as flank pain and hematuria. Hematuria was only present in 5 (33 per cent). Of the 15 patients with urologic findings the correct diagnosis was made in 9 (60 per cent), which is well above the average. In 2 of the 3 patients with gross hematuria in the present series, the correct diagnosis was made.

Halprin[64] reported a case of dissecting aneurysm associated with bilateral occlusion of both renal arteries, which presented the picture of uremia. Buckley[65] reported 2 patients with involvement of the renal arteries, both of whom had gross hematuria. Davis and his associates[66] described a patient with dissection of both renal arteries, who was thought to have acute nephritis.

Hematuria apparently is not a common finding in persons with dissecting aneurysm, but when it occurs it probably indicates dissection of one or more renal arteries with thrombosis and infarction. It may also be due to a concomitant malignant nephrosclerosis.

*Nonprotein Nitrogen.* Nonprotein nitrogen determinations were made in 9 patients, 7 of whom were found to have elevated values ranging from 47 to 85 mg. per 100 cc. of blood. In 3 of these with elevated values the renal arteries had been involved in the dissection; a fourth patient had malignant nephrosclerosis. Elevation of the blood nonprotein nitrogen may have a multiple pathogenic basis, resulting from a prerenal azotemia secondary to shock, caused by severe blood loss or dissection of the renal arteries with associated renal infarction, or, finally, from destruction and absorption of blood at the site of hemorrhage or external rupture.

*Pleural Fluid.* In those patients with pleural fluid, a diagnostic tap may reveal a bloody fluid, most frequently present in the left pleural cavity.

*Icteric Index.* Osgood, Gourley, and Baker[67] in 1936 first called attention to the presence of icterus in a patient with a dissecting aneurysm. The elevation was thought most likely a result of increased bilirubin production from the site of hemorrhage. Clinical icterus is usually absent, but occasionally it may be detected, especially when there is slow hemorrhage into the mediastinum or retroperitoneal space. Clinical icterus was detected in one of the patients in our series. The icteric index was 18. Unfortunately, the test was not performed in any of the other patients, so its value in the diagnosis of dissecting aneurysm cannot be properly determined.

*Serum Amylase.* In 2 patients an elevated serum amylase was detected. Both of these had abdominal pain and were suspected of having acute pancreatitis. One of these whose serum amylase was 300 units was subjected to an exploratory operation with the preoperative diagnosis of a perforated peptic ulcer with a contiguous pancreatitis. The operative findings were not remarkable, except for small-bowel distension. At autopsy there was found a dissecting aneurysm involving the superior mesenteric artery with hemorrhage about the head of the pancreas. In the other patient the serum amylase value was 500 units. In this patient the dissection of the aorta had only extended inferiorly to the beginning of the lower third of the thoracic aorta. The pancreas appeared grossly normal. No other reports of elevation of serum amylase in association with dissecting aneurysm were found in the literature.

## Diagnosis

Willius[69] stated that the diagnosis of dissecting aneurysm was not made often because of the infrequence of its occurrence, the variations in the clinical manifestations with the absence of a characteristic syndrome, and limited usefulness of special diagnostic adjuncts. It is our belief that the incidence of correct diagnosis can be and is being improved, and that from the study of large series of patients, such as the present group, the entity no longer appears bizarre, but falls into various syndromes which can often be readily recognized.

Of the 58 patients in this series who were seen from 1935 to 1947, the correct diagnosis was made in 16 (28.5 per cent). Obviously, this is not a startlingly high percentage of correct diagnosis. David, McPeak, Vivas-Salas, and White[1] reported recently an incidence of correct diagnosis in 7 of 17 cases (41 per cent), these cases having been observed at the Massachusetts General Hospital from 1935 to 1946. Shennan[14] was only able to report a correct antemortem diagnosis in 2 per cent of some 300 cases reviewed up to 1934. Emery[70] recently has reported 24 cases from Australia, none of which were correctly diagnosed. Reich[71] in a recent review from a large general hospital, reported 19 cases, only 2 of which had been correctly diagnosed antemortem.

In the present series, in cases studied between 1935 and 1940 the correct diagnosis was made in 18.7 per cent; in those studied between 1941 and 1947, a correct diagnosis was made in 30.9 per cent. Although this is not statistically significant it seems to indicate a trend of increasing accuracy in diagnosis with respect to dissecting aneurysm.

*Summary of the Diagnostic Features of Dissecting Aneurysm.* The various clinical features

of dissecting aneurysm have been described in some detail. These may be summarized as:

1. A previous history of hypertension is frequently elicited.

2. The onset is usually sudden and dramatic, with a history of severe, agonizing pain in the chest or abdomen, radiating most frequently to the back or down into the abdomen. Radiation to the extremities is not common, but of diagnostic value when present. Less often, the onset may be marked by syncope or unconsciousness.

3. Clinical shock, with either lowered or elevated blood pressure, is usually present at the onset.

4. Neurologic symptoms were present in 19 per cent of the patients, and varied from onset with syncope, dizziness, unconsciousness, or hemiplegia, all due to interruption of the cerebral blood supply, to transient weakness and anesthesia of one or more extremities due to ischemia of peripheral nerves or to interference with the blood supply to the spinal cord.

5. Aortic diastolic murmurs were present in 27.5 per cent of this series of patients. The appearance of a diastolic aortic murmur with aneurysmal dilatation of the ascending aorta, severe chest or abdominal pain, and negative serologic reactions is almost pathognomonic of dissecting aneurysm. Other investigators report the incidence of aortic diastolic murmurs as high as 56 per cent.

6. Inequalities of pulse and blood pressure recordings were found in 19 per cent of the patients.

7. Renal symptoms, such as oliguria, flank pain, and hematuria, when present, facilitate the diagnosis. They are usually due to dissection of the renal arteries, but may also be due to primary renal disease.

8. The most common electrocardiographic tracing encountered is that characteristic of left ventricular strain. In equivocal cases the absence of the pattern of myocardial infarction is in favor of the diagnosis of dissecting aneurysms in preference to that of coronary occlusion. The pattern of acute coronary occlusion does not rule out the possibility of dissecting aneurysm. The occurrence of varying patterns of myocardial ischemia, acute pericarditis, and uremia in association with dissecting aneurysm has been discussed. All the electrocardiograms (40 patients) showed abnormality. A normal pattern is unlikely in persons with dissecting aneurysm.

9. Chest x-ray examinations were performed on 20 patients. The value of the finding of a widened supracardiac shadow, progressive enlargement of the ascending or descending aorta, the double-barrelled shadow, and similar changes has been discussed. Twenty per cent of the patients had left pleural effusions. Cardiac enlargement, which is left ventricular in type, is often present.

10. Other laboratory data, such as the findings of anemia, leucocytosis, hematuria, elevated icteric index, and elevated serum amylase, have value in ascertaining the correct diagnosis.

## Prognosis

The duration of survival has already been discussed (table 2). In our series of 58 patients, 21 (36.2 per cent) died within forty-eight hours of the onset, 22 (35 per cent) survived three to sixty days, and 15 (25.9 per cent) survived three months to eight years. These statistics indicate a much better outlook than do those usually given. Weiss, Kinney, and Maher[63] felt that healing takes place in about 10 per cent of cases, whereas we found it in 25.9 per cent. Actually, if the work of Mote and Carr[18] is considered, the actual number of patients with dissecting aneurysm dying within the first twenty-four to twenty-eight hours would be greatly increased and correspondingly the percentage surviving into the "healed" type decreased. Mote and Carr reported 60 deaths due to acute dissecting aneurysms recorded at the San Francisco Coroner's Office over a five-year period.

## Treatment

The management of these patients in many ways is not unlike that of patients with coronary occlusion. Absolute bed rest with feeding of the patient should be enforced for a long period of time. The pain should be relieved by the liberal use of morphine, employing large doses if necessary. Oxygen should be used continuously for dyspnea and shock, or if signs of occlusion of vessels persists. In profound shock, transfusions of whole blood may be life-saving. Fluids should be administered slowly and the

diet should be light and bland, as in coronary occlusion. Regulation of diet and bowel movements should be such that the patient is spared undue muscular effort. Sedation, preferably that of chloral hydrate, should be used as indicated. The patient should not be subjected to repeated x-ray examination and fluoroscopy in an effort to find out what is going on in the mediastinum. A bedside plate is indicated. Operative re-entry in those cases which have resulted in occlusive disease of the iliacs has been reported by Gurin, Bulmer, and Derby.[68] This may prove not only beneficial in relieving the local obstruction but may prolong life and result in a greater percentage of "chronic or healed" dissecting aneurysms. Anticoagulant therapy (such as heparin or dicumarol treatment) is definitely contraindicated.

## Summary

The literature has been reviewed, and the findings in 58 cases of dissecting aneurysm from the Los Angeles County Hospital from 1935 to 1947 have been presented, with emphasis on distinguishing clinical features and an attempt at clinicopathologic correlation. Particular stress has been placed on the frequency of the aortic diastolic murmur and the mechanism of its production. Electrocardiograms were made in 40 of the patients, and these have been carefully reviewed and classified in an effort properly to evaluate the electrocardiogram in the diagnosis of dissecting aneurysm.

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# A Study of the Venous Pulse in Tricuspid Valve Disease

*By* Addison L. Messer, M.D., John Willis Hurst, M.D., Maurice B. Rappaport, E.E., and Howard B. Sprague, M.D.

Diagnosis of lesions of the tricuspid valve is often difficult. Mechanically, however, the action of this valve is capable of study through its effect upon the peripheral veins, somewhat as the disturbances of the aortic valve are reflected in the peripheral arteries. The conditions to be differentiated are "organic" versus "functional" regurgitation, and obstruction of the valve from rheumatic stenosis. Graphic records of the venous pulse with suitable reference tracings may make this possible.

THE PRESENCE of an unusually large positive ventricular systolic pulsation in the internal jugular veins has been recognized for years as a sign of tricuspid regurgitation. White and Cooke[1] have suggested that, when this type of pulsation has been present for months or years without significant congestive heart failure, tricuspid stenosis also may be present. The value of noting the degree of venous distention and the presence or absence of venous pulsation is generally appreciated, but it is rare that actual timing of the pulse waves by simultaneous auscultation of the heart is attempted. Such observations can be made without difficulty unless the heart rate is rapid.

The clinical and pathologic features of tricuspid stenosis and regurgitation have been adequately discussed.[3–20] In all of the cases reported the factors leading to the correct diagnosis ante mortem consisted in a high index of suspicion and the recognition of the *peripheral manifestations* of this lesion. When other peripheral signs of tricuspid regurgitation are present, i.e., expansile pulse of the liver, ascites, venous engorgement, and edema; the manifestations in the jugular veins will always be present. It is for this reason that careful observations of the character of the pulsation in the jugular veins is one of the most important clues to abnormality of the tricuspid valve.

Description of the normal venous pulse and the technic of graphic recording can be found in the monographs of Wiggers[21] and Groedel.[22] There are three important points in observing or recording the venous pulse. First, the *internal* jugular, not the external or superficial, is the most suitable vein to use. Second, because this vein lies beneath the sternocleidomastoid muscle it is important that there be no tension in this muscle, for tension can completely obliterate or greatly alter the pulsations. It is best to have the subject's head facing forward or rotated slightly toward the side used for recording or observing. The head should never be rotated greatly as this will cause excessive tension in the neck muscles. Third, the upper half of the patient's body must be elevated to the point where the veins will be seen to empty and fill with the greatest amplitude. This position must be determined individually for each patient.

Venous pulsation can be distinguished from arterial by the general configuration of rounded undulating waves of the former, by the fact that arterial pulsation is easily palpable whereas venous pulsation is not, and, most important, by timing the waves with the heart sounds during auscultation.

The venous pulse in tricuspid regurgitation tends to lift the sternocleidomastoid muscle slowly during the latter part of ventricular diastole; this elevation becomes suddenly more marked during systole and is followed by an abrupt and pronounced collapse of the vein immediately after the second sound. This diastolic collapse of the vein is one of the most striking features of tricuspid regurgitation.

We are reporting 10 patients who presented this type of pulsation. In 6 of the patients tricuspid regurgitation was associated with acute or chronic right ventricular failure and dilatation of the tricuspid valve ring without evidence of organic valvular disease. Four pa-

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tients had rheumatic heart disease with multiple valvular involvement, and, in addition to the abnormal venous pulse, had other peripheral signs of tricuspid valve disease. A diastolic murmur at the lower end of the sternum could be heard or recorded in all patients of the latter group. A comparison of the graphic records of those patients in whom tricuspid regurgitation was associated with dilatation of the right ventricle without stenosis of the valve and of those in whom tricuspid regurgitation and stenosis were thought to be present, showed certain differences.

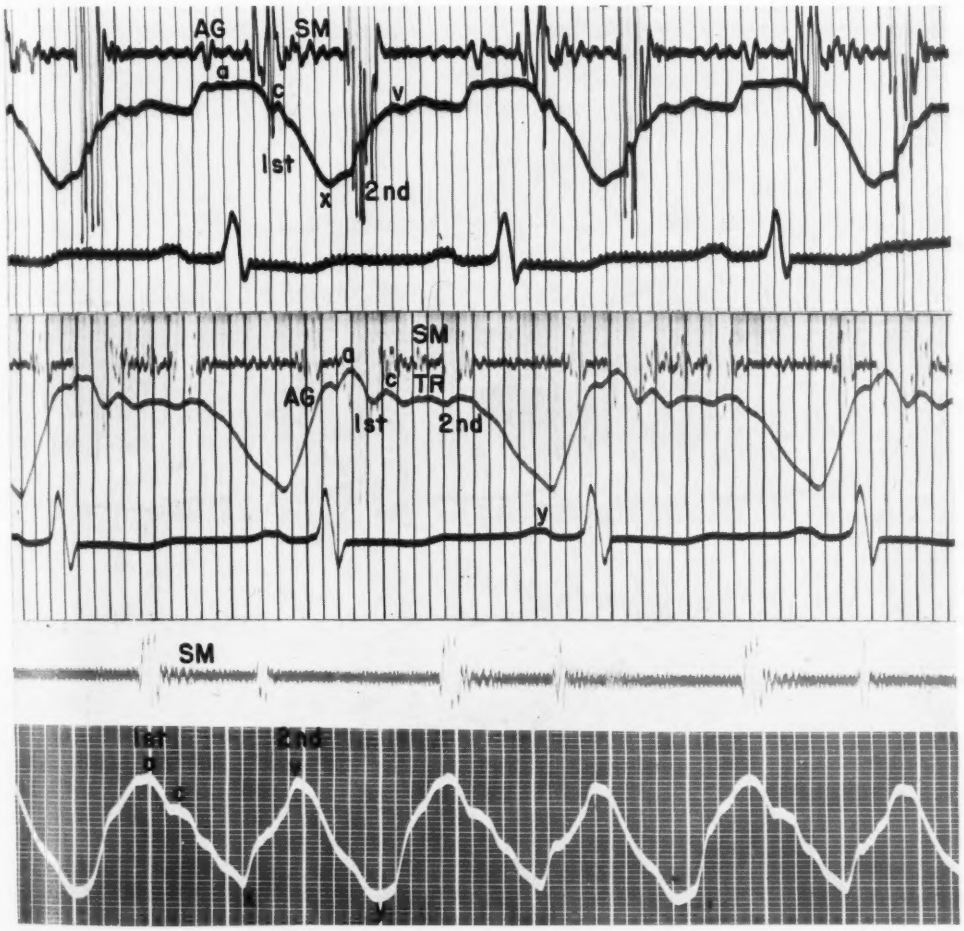


FIG. 1.—*A* (top tracing). Phonocardiographic, venous pulse, and electrocardiographic tracings made during heart failure unassociated with tricuspid regurgitation. A.G indicates presystolic (auricular) gallop; point x indicates the normal systolic collapse.

*B* (middle tracing). Tracings made three and one half months following those shown in *A* after tricuspid regurgitation had developed. The venous pulse shows an absence of the normal systolic collapse which has been replaced by a positive systolic wave, TR, owing to tricuspid regurgitation. The diastolic collapse, point y, is now quite striking.

*C* (bottom tracing). Phonocardiogram and venous pulse tracing, made after the congestive failure had cleared, showing a normal systolic (x) and disatolic (y) collapse.

The tracings reproduced were made at 75

mm. per second with a Sanborn Tri-Beam Stethocardiette and the venous pulse was recorded by means of a crystal microphone.[23, 24] An electrocardiogram and phonocardiogram were recorded as reference tracings; the latter proved to be of greater value than the former because it provides the most accurate reference tracing for the beginning and ending of mechanical systole as well as for other events during the cardiac cycle.

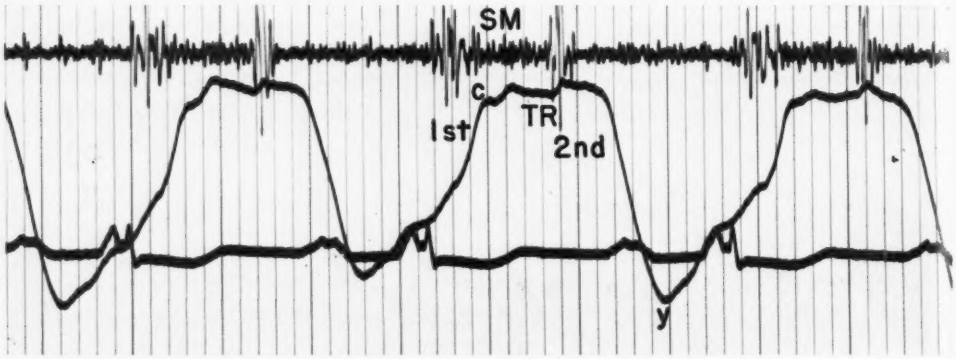


FIG. 2.—Phonocardiogram, venous pulse record, and electrocardiogram. There is a low energy systolic murmur (SM). The venous pulse shows a plateau-like positive wave following the c wave and replacing the normal systolic collapse; this wave (TR) is due to tricuspid regurgitation and ends in an abrupt diastolic collapse (y) when the tricuspid valve opens.

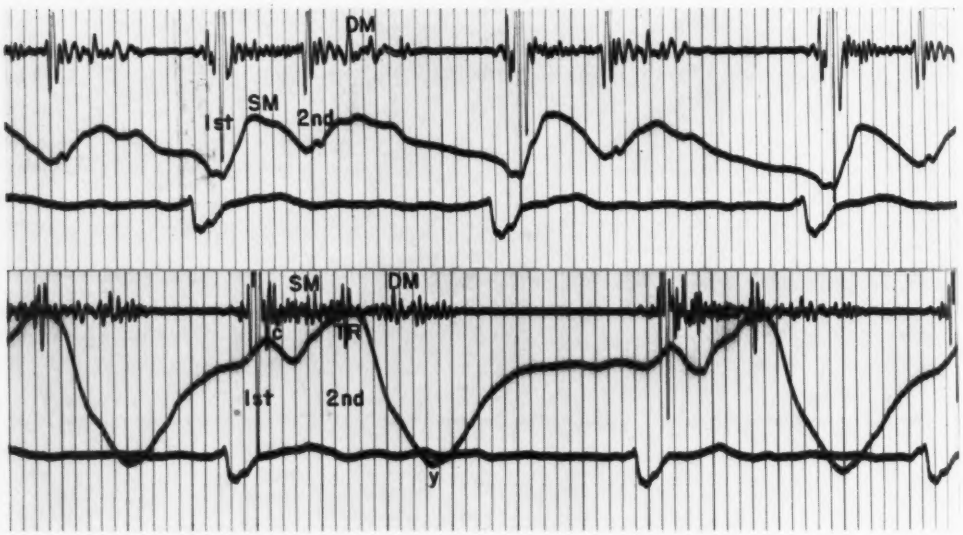


FIG. 3.—*A* (top tracing). Phonocardiogram, arterial pulse record, and electrocardiogram. The phonocardiogram shows a low energy systolic murmur (SM) and a low-frequency diastolic murmur (DM) at the apex.

*B* (bottom tracing). Phonocardiogram, venous pulse record, and electrocardiogram. The phonocardiographic tracing made over the tricuspid area shows a systolic murmur (SM) and diastolic murmur (DM). The venous pulse has a positive systolic wave (TR) due to tricuspid regurgitation. The deep diastolic collapse (y) coincides with the diastolic murmur.

Figures 1 and 2 illustrate venous pulse tracing from two patients with right ventricular dilatation and variable tricuspid regurgitation without evidence of stenosis. In figure 1, *A*, the venous pulse shows no evidence of tricuspid regurgitation although the patient had congestive failure with pulmonary congestion, high venous pressure, and peripheral edema. In figure 1, *B*, made after the patient had a sudden weight gain of 25 pounds associated with a marked increase in edema and ascites but little increase in dyspnea, the venous pulse shows tricuspid regurgitation. Figure 1, *C*, made after partial compensation, shows the normal systolic collapse of the venous pulse indicating a return of competence of the tricuspid valve. Figure 2 is an illustration of the venous pulse showing tricuspid regurgitation associated with dilatation of the tricuspid valve ring in another patient.

Figures 3 and 4 are examples of the type of venous pulse tracings we have obtained from patients with rheumatic heart disease and multiple valvular lesions with evidence of tricuspid regurgitation. None of these patients presented acute or recent congestive failure. This type of venous pulse together with chronic enlargement of the liver was present for several months to over a year without marked dyspnea or orthopnea being manifest in these patients

## Discussion

The positive late systolic wave is not an exaggeration of any of the normal waves in the jugular pulse but replaces what would normally be a negative wave or collapse of the vein. It is due to the regurgitation of blood through an incompetent tricuspid valve. This transmission to the jugular vein prevents the normal late systolic emptying of the veins into the venous reservoir within the thorax and is responsible for the systolic distention of these veins. At the end of systole there may occur some decline in the positive wave of regurgitation. However, the deep diastolic collapse does not occur until the tricuspid valve opens. This collapse always coincides with the diastolic murmur associated with blood flowing through the valve when tricuspid stenosis is also present.

A comparison between the graphic tracings of the patients with tricuspid regurgitation

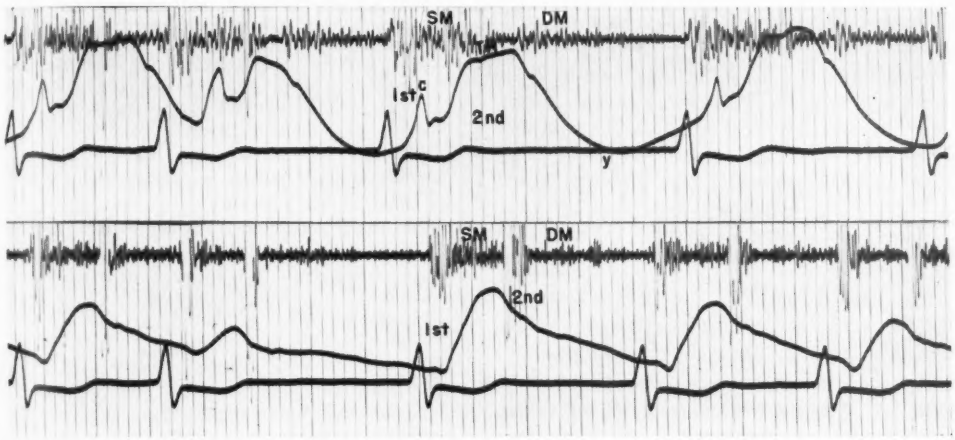


Fig. 4.—*A* (top tracing). Phonocardiogram, venous pulse record, and electrocardiogram. The phonocardiographic tracing made at the apex shows a systolic murmur (SM) and a diastolic murmur (DM). Following the c wave in the venous pulse there is a positive wave (TR) due to tricuspid regurgitation with a diastolic collapse (y) coinciding with the diastolic murmur.

*B* (bottom tracing). Phonocardiogram, carotid pulse record, and electrocardiogram. These tracings show the difference between the form of the arterial and venous pulse in the neck. The phonocardiogram was made over the tricuspid area.

due to dilatation of the tricuspid ring and those of patients with organic disease of the tricuspid valve demonstrates certain differences. In the latter group the positive systolic wave begins at a definite interval after the c wave, the rise is slower than in the former group, and the peak tends to occur somewhat later. The diastolic collapse is slower; however, the onset and maximum collapse coincide with the diastolic murmur associated with ventricular filling. The factors responsible for the delay in the rise of the systolic regurgitant wave seem to consist of (1) incomplete filling of the right ventricle due to the valvular obstruction and (2) a similar impedance at the valve during regurgitation, associated with transmission of the wave against a higher atrial pressure. This is shown in figure 4. The second systole occurs relatively early and the delay in the systolic venous wave (1A) is evident. However, the abrupt diastolic collapse occurs with the opening of the tricuspid valve and the onset of the diastolic murmur. When diastole is short, in the presence of mitral or tricuspid valve stenosis, the atria do not have sufficient time to empty and, at the onset of systole, the ventricles are less well filled than under normal conditions. The result is a smaller regurgitant stroke volume against a higher atrial pressure.

In those patients in whom tricuspid regurgitation is due to dilatation of the valve ring there is no mechanical interference in ventricular filling; hence, although the venous and atrial pressures may be high, the systolic wave of regurgitation occurs earlier in systole. In our records from patients with tricuspid regurgitation due to severe right-sided heart failure, the early rise of the positive systolic wave in the venous pulse was a constant feature, although the heart rates were relatively rapid and comparable to the faster rates of those patients thought to have tricuspid stenosis.

### *Conclusions*

1. The normal phlebogram from the internal jugular vein shows a negative wave, due to collapse of the venous pulse in the latter part of ventricular systole, when the veins empty into the thoracic venous reservoirs.

2. Tricuspid regurgitation replaces this negative wave with a positive wave as the veins distend from backflow, and it is followed by an abrupt diastolic venous collapse.

3. When tricuspid regurgitation is combined with tricuspid stenosis there is a delay in the appearance of this positive wave following the c wave, the rise of the wave is slower, the peak occurs later, and the diastolic collapse is slower.

4. These differences in the venous records in "functional" tricuspid regurgitation as contrasted with those from patients with organic tricuspid stenosis are accounted for by impedance effects due to the stenosis.

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# Myocardial Lesions Produced by Digitalis in the Presence of Hyperthyroidism: An Experimental Study

*By* William H. Dearing, M.D., Arlie R. Barnes, M.D., and Hiram E. Essex, Ph.D.

Calculated therapeutic doses of digitalis and its derivatives did not produce demonstrable microscopic changes in the myocardium of experimental animals. Toxic doses of digitalis (twice a therapeutic dose) induced myocardial lesions in animals. In those animals with experimentally induced mild to moderate hyperthyroidism, calculated therapeutic doses of digitalis did produce myocardial lesions. Toxic doses of digitalis administered to animals with mild to moderate hyperthyroidism caused extensive degenerative changes in the myocardium or promptly killed the animals without associated microscopic lesions.

THIS INVESTIGATION was undertaken in order to determine whether myocardial lesions are produced more readily in animals with induced hyperthyroidism than in normal animals when various doses of digitalis are administered. A previous study[1] had shown that calculated therapeutic doses of digitalis fail to produce any demonstrable organic lesions in the myocardiums of normal animals.

## Review of Literature

Histologic changes in the myocardiums of animals with experimental hyperthyroidism were reported in at least eight articles from 1913 to 1935.[2-9] These histologic changes ranged from minor fatty degeneration in the muscle fibers to frank necrosis of the muscle fibers with exudative cellular infiltration. Fibroblasts and fibrosis have been described as replacing destroyed myocardial bundles. Lewis and McEachern[10] in 1931, Rake and McEachern[11, 12] in 1931 and David[13] in 1938, however, were unable to demonstrate specific myocardial lesions in animals with experimental hyperthyroidism. Fahr[14] in 1916, Goodpasture,[15] Hashimoto,[3] and Fahr and Kuhle[16] in 1921 and Goodall and Rogers[17] in 1927 found evidence of histopathologic changes in the hearts of patients with hyperthyroidism. Baust[18] and Lahey[19] in 1930 considered that pathologic changes do not occur in the myocardiums of patients who have hyperthyroidism. Various other authors,[20-23] however, have stated that heart failure does occur in hyperthyroidism without any evidence of coexisting cardiac disease (coronary sclerosis, syphilis, or rheumatic carditis), but that it is not encountered often. The voluminous literature dealing with cardiac dilatation, cardiac hypertrophy, metabolism, and chemical and physiologic changes in clinical and experimental hyperthyroidism will not be mentioned because it is beyond the scope of this article.

Histologic changes produced in the myocardiums of animals by various preparations of digitalis have been described frequently since 1904[1, 24-32] and many investigations have dealt with the role of digitalis in hyperthyroidism. Foster,[33] Sturgis,[34] Grant,[35] and others in 1925 and 1926 reported that digitalis was of value in hyperthyroidism when auricular fibrillation without heart failure was present. In 1932, Barker and his associates[36] stated that digitalis was less effective in auricular fibrillation associated with hyperthyroidism than with auricular fibrillation associated with any other condition. Plummer[37] in 1925 noted that administration of digitalis increased the mortality rate in cases of hyperthyroidism. This observation, in part, furnished the stimulus for this investigation. Many investigators[38-50] have reported electrocardiographic changes in hyperthyroidism which are, however, not characteristic of the disorder. The changes include tachycardia, various cardiac arrhythmias (premature contractions, paroxysmal auricular and ventricular tachycardia, auricular flutter, auricular fibrillation, and heart block). There were high P waves, tall T waves, decrease in amplitude of T waves, negative T waves, elevated RS-T segments, and depressed RS-T segments. The majority of investigators have concluded that there is no specific change in the electrocardiogram which is characteristic of hyperthyroidism.

The electrocardiographic changes in man and animals following the administration of digitalis also have been recorded by many investigators from 1909 to 1947.[51-83] It will be seen from their papers that digitalis may not induce any significant change in the electrocardiogram or it may produce sinus bradycardia, sinus tachycardia, prolonged P-R interval, pulsus bigeminus, increase in the height of the T waves, decrease in the height of the T waves, negative T waves, elevation of the RS-T segment, depression of RS-T segment, and so forth, depending on the circumstances and the dosage of digitalis.

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## Methods

Cats which appeared to be in good health were used for our studies. Each animal was trained to lie quietly on its right side while electrocardiograms were taken. A control tracing was made each day until the contour of the tracing was fairly constant, and the animal was trained satisfactorily.

The animals were weighed and then fed thyroid extract, double strength U.S.P., mixed with fresh meat each day. This dose of double strength U.S.P. thyroid extract varied from 1.0 to 2.0 Gm. per kilogram of body weight. When the animal failed to eat the food containing the thyroid extract, 1.0 to 2.0 mg. of thyroxin (prepared by Dr. E. C. Kendall) per kilogram of body weight was administered parenterally each day. An endeavor was made to render the animals moderately hyperthyroid, so that each animal would lose from 18 to 28 per cent of its weight during the course of the hyperthyroidism. Attempts were made in a few animals to measure the increase in the metabolic rate after administration of thyroid extract or thyroxin, but the process was considered too time-consuming and was discarded in favor of methods which permitted us to study a larger series of animals in which the degree of hyperthyroidism was estimated on basis of loss of weight, tremor, and heart rate.

After evidence of hyperthyroidism was exhibited, various preparations of digitalis were administered parenterally in a single dose. Digitalis (2.0 cc. = 1.0 cat unit = 0.8 U.S.P. XII digitalis units), digitoxin (0.2 mg. per c. c.: 0.42 mg. per kilogram of cat = minimal lethal dose), and lanatoside A (0.35 mg. per kilogram of cat = minimal lethal dose) were the preparations used. In order to maintain hyperthyroidism after digitalis was given, 1.0 mg. of thyroxin per kilogram body weight was injected daily into each animal.

Electrocardiograms were made at least once a week during the interval of hyperthyroidism and almost every day after the digitalis was administered.

When the course of studies was completed on each animal, the animal was killed quickly with ether or chloroform. Postmortem examination was performed promptly; blocks of tissue were removed from the heart and fixed in formalin. Sections of the heart were prepared, mounted on glass slides, and stained with hematoxylin and eosin for study.

Control animals were treated exactly like the other animals except that the controls did not receive digitalis or preparations of thyroid. A series of animals was studied which received preparations of thyroid without any digitalis.

## Results

### *Histologic Studies*

The animals used in these studies will be grouped, for the purpose of presentation, as follows: (1) Healthy control animals not treated with drugs, (2) animals with induced hyperthyroidism, (3) animals given calculated therapeutic or toxic doses of digitalis, and (4) animals with induced hyperthyroidism which received digitalis in various doses.

*Normal Animals.* Thirty-two healthy cats that had not received any drugs served as control animals. Examination of the myocardiums of these animals revealed no significant histologic abnormalities.

Fig. 1.—Degenerative changes in myocardial fibers of animals with severe hyperthyroidism (hematoxylin and eosin ×275).

*Animals with Induced Hyperthyroidism Only.* These were divided into two groups: (1) those with moderate hyperthyroidism (loss of from 18 to 28 per cent of total weight) produced by administration of thyroid extract or thyroxin for ten to twenty-six days and (2) those with severe hyperthyroidism (loss of from 25 to 51 per cent of total weight) induced by doses of thyroid extract or thyroxin or both in nine to twenty-seven days. All except one of the animals with moderate hyperthyroidism were

killed while all those with severe hyperthyroidism died.

No myocardial lesions were found in the 8 animals with moderate hyperthyroidism. These animals are the controls for our studies on the effect of digitalis in hyperthyroidism.

The effect of severe hyperthyroidism on the myocardium was studied since changes in myocardial tissue have been described in the presence of hyperthyroidism in man and animals. Animals with severe hyperthyroidism could not be used as controls for our studies since the animals became too ill, the duration of the study could not be satisfactorily controlled, and the animals died readily of concurrent respiratory infections or of the induced metabolic disorder. In 2 of the 8 animals with severe hyperthyroidism, lesions developed. These consisted of scattered zones of destructive changes in the myocardial fibers (fig. 1).

TABLE 1.—*Effect of Calculated Therapeutic Doses of Digitalis on Histologic Changes in the Myocardium of Animals with Hyperthyroidism*

| Degree of Hyperthyroidism | Administration of Thyroid | | | Dose of Digitalis (per cent M.L.D.* and drug) | Duration of Study After Digitalis (days) | Termination | Histologic Changes in Myocardium |
|---|---|---|---|---|---|---|---|
| | Weight Before and After | | Days | | | | |
| | Kg. | Per cent lost | | | | | |
| Moderate | 3.8–3.2 | 16 | 28 | 30; digalen | 14 | Killed | No |
| Mild | 2.6–2.3 | 12 | 28 | 30; digalen | 14 | Killed | No |
| Moderate | 2.2–1.8 | 18 | 25 | 30; digalen | 2 | Died | No |
| Moderate | 3.7–3.0 | 27 | 25 | 30; digalen | 10 | Killed | No |
| Moderate | 3.6–2.8 | 22 | 21 | 30; digitoxin | 1 | Died | No |
| Moderate | 3.4–2.7 | 20 | 21 | 30; digitoxin | 10 | Killed | No |
| Moderate | 3.0–2.2 | 26 | 21 | 30; digalen | 10 | Killed | No |
| Moderate | 1.8–1.5 | 17 | 21 | 30; digalen | 10 | Killed | No |
| Mild | 2.1–1.8 | 14 | 25 | 30; digalen | 10 | Killed | Yes + |
| Moderate | 3.0–2.4 | 20 | 21 | 30; digalen | 10 | Killed | Yes + |
| Moderate | 1.5–1.1 | 26 | 21 | 30; digalen | 6 | Died | Yes ++ |
| Moderate | 3.4–2.6 | 24 | 21 | 30; digalen | 7 | Died | Yes ++ |
| Moderate | 2.4–1.9 | 20 | 21 | 30; digitoxin | 10 | Killed | Yes ++ |
| Moderate | 2.7–2.2 | 18 | 21 | 30; digitoxin | 10 | Killed | Yes +++ |
| Moderate | 2.3–1.8 | 20 | 21 | 30; digitoxin | 14 | Killed | Yes +++ |
| Mild | 3.2–2.8 | 13 | 21 | 30; digitoxin | 14 | Killed | Yes ++++ |
| Moderate | 3.2–2.4 | 22 | 21 | 30; digitoxin | 10 | Killed | Yes ++++ |
| Moderate | 4.7–3.3 | 31 | 25 | 30; digalen | 9 | Died | Yes ++++ |

* M.L.D. = Minimum lethal dose.

*Animals which Were Given Calculated Therapeutic or Toxic Doses of Digitalis.* It has been shown by the authors[1] that calculated therapeutic doses of digitalis did not produce evidence of histologic changes in the myocardium of 24 animals. In the present studies, 6 normal animals were given intravenously 30 per cent of the minimal lethal dose of digitoxin but no evidence of myocardial lesions was found when these animals were killed twelve days after the drug was administered. In the previous publication we noted that toxic doses of digitalis can produce myocardial lesions in animals. Histologic changes in the heart were produced by digitalis whole leaf or crystallin products of digitalis (digitoxin, lanatoside A, lanatoside B, and lanatoside C). In these experiments, 60 to 80 per cent of the minimal lethal dose of digitalis was necessary to produce myocardial lesions.

The important point to note here is that doses of digitalis which were calculated on the basis of body weight to correspond to those given therapeutically to man failed to produce any histologic changes in the myocardiums of the animals.

*Animals with Induced Hyperthyroidism which Received Digitalis.* Calculated therapeutic doses of digitalis given to animals with mild or moderate hyperthyroidism can produce myocardial

lesions as shown in table 1. It is to be recalled that comparable doses of digitalis did not induce any evidence of structural changes in the heart of animals without hyperthyroidism.

Demonstrable histopathologic changes developed in the heart muscles of 10 of the 18 animals with mild or moderate hyperthyroidism which received calculated therapeutic doses of digitalis (fig. 2). Two of these 18 animals died within one to two days after administration of the digitalis preparation. In previous studies[1] we showed that it was necessary for animals to live for at least five days, even after highly toxic doses of digitalis, before histologic changes could be demonstrated in the heart muscle; hence it was not likely that these 2 animals which died so soon would exhibit any myocardial lesions.

Smaller doses of digitalis (5 to 20 per cent of the minimal lethal dose) were much less likely to produce histologic changes in the myocardium of animals with mild to moderate hyperthyroidism as shown in table 2. Toxic doses of digitalis, however, either killed the hyperthyroid animal before sufficient time had elapsed for the development of cellular necrosis in the heart muscle or the animal died within a few

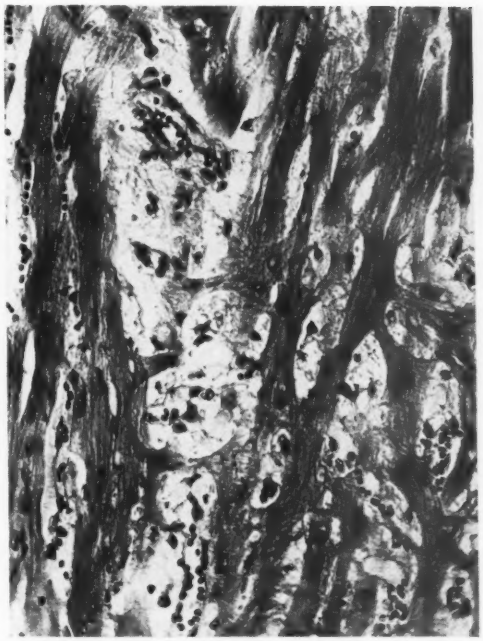

FIG. 2.—Degenerative changes in myocardium of animal with moderate hyperthyroidism which received calculated therapeutic dose of digitalis (hematoxylin and eosin ×275).

TABLE 2.—*Effect of Small Doses of Digitalis on Histologic Changes in the Myocardium of Animals with Hyperthyroidism*

| Degree of Hyperthyroidism | Administration of Thyroid | | | Dose of Digitalis (per cent M.L.D.* and drug) | Duration of Study After Digitalis (days) | Termination | Histologic Changes in Myocardium |
|---|---|---|---|---|---|---|---|
| | Weight Before and After | | Days | | | | |
| | Kg. | Per cent lost | | | | | |
| Moderate | 4.3–3.6 | 16 | 28 | 5; digalen | 14 | Killed | No |
| Mild | 4.4–3.9 | 11 | 28 | 5; digitoxin | 14 | Killed | No |
| Moderate | 4.6–3.7 | 19 | 28 | 5; digitoxin | 14 | Died | No |
| Moderate | 1.8–1.4 | 22 | 25 | 5; digitoxin | 10 | Killed | No |
| Moderate | 3.7–2.9 | 22 | 25 | 5; digitoxin | 10 | Killed | No |
| Moderate | 3.8–2.9 | 23 | 25 | 5; digitoxin | 10 | Killed | No |
| Mild | 2.6–2.2 | 15 | 25 | 5; digitoxin | 10 | Killed | No |
| Mild | 2.9–2.5 | 14 | 25 | 5; digitoxin | 10 | Killed | No |
| Moderate | 3.6–2.9 | 18 | 25 | 5; digitoxin | 10 | Killed | No |
| Mild | 2.0–1.8 | 10 | 25 | 5; digitoxin | 10 | Killed | No |
| Moderate | 3.0–2.2 | 27 | 21 | 5; digitoxin | 10 | Killed | No |
| Mild | 3.0–2.7 | 10 | 21 | 5; digitoxin | 10 | Killed | No |
| Moderate | 2.5–2.0 | 21 | 21 | 5; digitoxin | 10 | Killed | Yes + |
| Mild | 3.2–2.8 | 13 | 25 | 10; digitoxin | 25 | Killed | No |
| Moderate | 3.7–3 | 19 | 25 | 10; digitoxin | 25 | Killed | No |
| Mild | 4.2–3.8 | 9 | 28 | 20; digitoxin | 14 | Killed | No |
| Severe | 3.6–2.5 | 30 | 25 | 20; digitoxin | 10 | Killed | Yes ++ |

* M.L.D. = Minimum lethal dose.

days from extensive destructive changes in the myocardium (table 3 and fig. 3).

TABLE 3.—*Effect of Toxic Doses of Digitalis on Histologic Changes in the Myocardium of Animals with Hyperthyroidism*

| Degree of Hyperthyroidism | Administration of Thyroid | | | Dose of Digitalis (per cent M.L.D.* and drug) | Duration of Study After Digitalis (days) | Termination | Histologic Changes in Myocardium |
|---|---|---|---|---|---|---|---|
| | Weight Before and After | | Days | | | | |
| | Kg. | Per cent lost | | | | | |
| Mild | 2.1–1.9 | 9 | 26 | 60; digalen | 1 | Died | No |
| Moderate | — | | 25 | 60; digalen | 1 | Died | No |
| Moderate | — | | 25 | 60; digitoxin | 1 | Died | No |
| Severe | 1.8–1.2 | 33 | 21 | 60; digitoxin | 2 | Died | No |
| Severe | 3.0–2.1 | 30 | 21 | 60; digitoxin | 1 | Died | No |
| Moderate | 1.7–1.3 | 24 | 22 | 80; digitoxin | 5 | Died | Yes ++ |
| Mild | 2.8–2.3 | 14 | 21 | 60; lanatoside A | 6 | Died | Yes ++++ |
| Moderate | 2.6–2.0 | 23 | 25 | 60; digalen | 5 | Died | Yes ++++ |

* M.L.D. = Minimum lethal dose.

The myocardial lesions in hyperthyroid animals which received sufficient digitalis consisted of hemorrhage, cellular degeneration or necrosis, and inflammatory cellular exudates. Fibroblastic proliferation occurred if circumstances of the study permitted.

*Electrocardiographic Studies*

The animals in which hyperthyroidism was induced did not exhibit any characteristic electrocardiographic patterns; that is, the electrocardiographic changes were not constant and were not typical of hyperthyroidism to the exclusion of all other conditions. In the majority of the animals with hyperthyroidism, sinus tachycardia developed. At times, ventricular premature contractions, tall T waves, short T waves, negative T waves, elevated RS–T segments, and depressed RS–T segments were observed. Some of the electrocardiographic changes in the three standard limb leads when thyroid preparations had been administered to the animal for approximately three weeks are shown in figures 4 to 6.

When doses of digitalis, which were calculated not to exceed corresponding therapeutic doses for man, were given to animals with experimental hyperthyroidism, the following changes were noted with varying frequency among more than 500 electrocardiograms (each with three standard limb leads): (1) no significant alteration when compared to the control tracing; (2) sinus tachycardia; (3) sinus bradycardia; (4) ventricular premature contractions; (5) paroxysmal auricular or ventricular tachycardia; (6) ventricular fibrillation; (7) de-

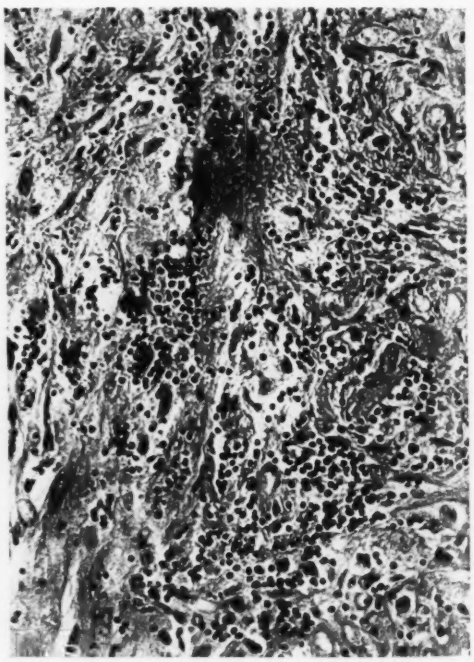

FIG. 3.—Extensive degenerative changes in myocardium of moderately hyperthyroid animal which received toxic dose of digitalis (hematoxylin and eosin ×275).

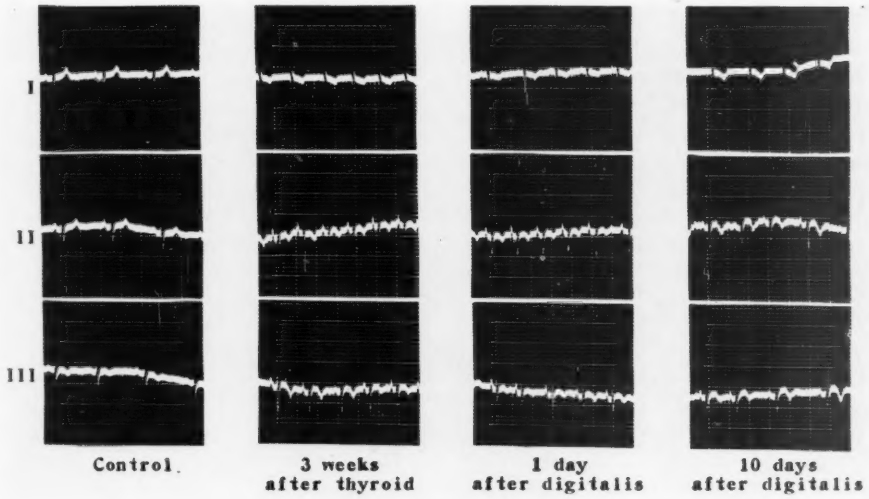


FIG. 4.—Series of electrocardiograms made on one animal comparing the control tracing with those made after three weeks of hyperthyroidism and then one day and ten days after a calculated therapeutic dose of digitalis was given. No histologic changes were found in the myocardium on the tenth day after digitalis was administered.

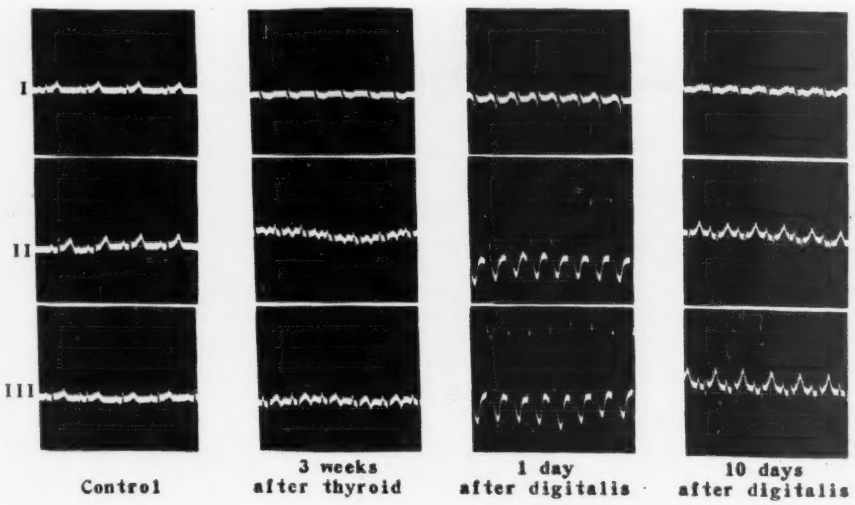


FIG. 5.—Series of electrocardiograms made on one animal comparing the control tracing with those made after three weeks of hyperthyroidism and then one day and ten days after a calculated therapeutic dose of digitalis was given. Definite myocardial lesions were found on the tenth day after digitalis was administered.

pressed RS–T segments in one or more leads, usually in Leads I and II or Leads II and III; (8) elevated RS–T segment in Leads I and II or Leads II and III; (9) decrease in height of T waves, and (10) negative T wave in Leads I and II, Leads II and III, or occasionally in all three leads.

We were unable to correlate any definite electrocardiographic pattern with myocardial lesions, although elevation of the RS–T segments as in figure 6 was usually associated with demonstrable cellular necrosis in the heart muscle. Negative T waves and depression of the RS–T segments are not necessarily indications of observable histologic myocardial lesions.

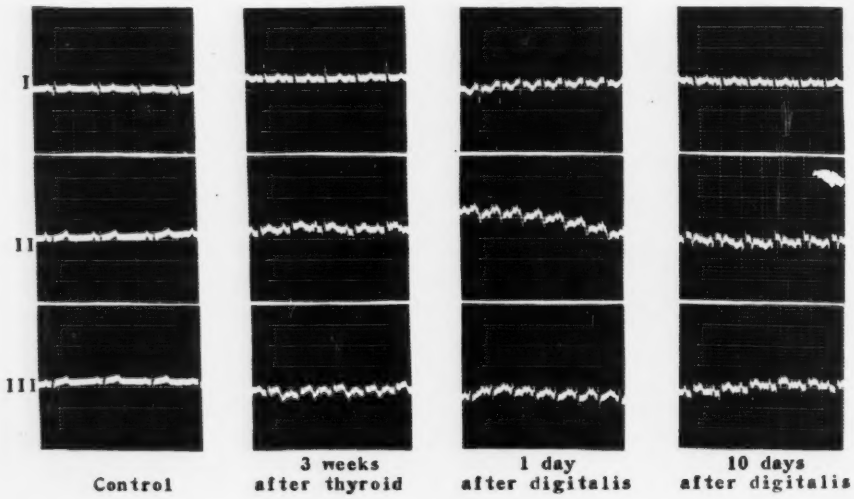


FIG. 6.—Series of electrocardiograms made on one animal comparing the control tracing with those made after three weeks of hyperthyroidism and then one day and ten days after a calculated therapeutic dose of digitalis was given. Definite myocardial lesions were found on the tenth day after digitalis was administered.

## COMMENT

It is apparent that digitalis in calculated therapeutic doses may produce myocardial lesions in animals with hyperthyroidism while the same dose of digitalis will not induce any demonstrable pathologic changes in the heart of normal animals.

It should be pointed out that certain sources of error exist in these studies: (1) We have estimated the degree of hyperthyroidism rather than performed an actual determination of the increase in the metabolic rate with special apparatus. (2) We have calculated the dose of digitalis for the cat on the basis of body weight of the animal and have compared it with the dose used for human beings on the basis of units of body weight. We have no way of knowing whether the cat and man are equally sensitive to digitalis. We think this statement applies to whole-leaf digitalis that has been standardized by the cat unit method or for crystallin products (digitoxin and the lanatosides) which have been prepared gravimetrically for administration. (3) The morphologic study of the myocardium does not indicate the multitude of chemical and metabolic changes that may occur in the myocardium of animals treated with thyroid preparations or with digitalis preparations. Our studies show that animals treated with these preparations may die without any demonstrable lesion having developed in the myocardium.

It was noted that the older the animal, the more likely it is to have changes in the myo-

cardium after digitalis has been administered. None of the animals had any signs or symptoms suggestive of cardiac decompensation.

## Summary

No demonstrable microscopic lesions were found in the myocardium of 32 normal animals to which drugs were not administered. Thyroid extract (double strength U.S.P.) and thyroxin produced myocardial lesions in 2 animals of 8 animals with severe hyperthyroidism but did not induce any demonstrable pathologic change in the myocardiums of 8 animals with moderate hyperthyroidism. Calculated therapeutic doses of digitalis did not produce definite myocardial lesions in 30 animals without hyperthyroidism but did induce myocardial lesions in 10 out of 18 animals with mild to moderate hyperthyroidism.

Toxic doses of digitalis, when given to animals with mild or moderate hyperthyroidism, caused extensive degenerative changes in the myocardium if the animals survived more than five days or resulted in death within one to two days among animals in which microscopic changes could not be found in the myocardium.

The myocardial lesions produced by digitalis in animals with hyperthyroidism consisted of hemorrhage, degeneration or necrosis of myocardial fibers, and inflammatory cellular exudates. Fibroblastic proliferation occurred if circumstances permitted healing of the damaged myocardium.

Numerous electrocardiographic changes were noted in the presence of experimental hyperthyroidism both when digitalis had been administered and when it had not. None of the electrocardiographic changes could be ascribed to any pattern which was characteristically associated with the myocardial lesions.

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# Circulatory Adjustments to the Hypoxemia of Congenital Heart Disease of the Cyanotic Type

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In a limited number of subjects having hypoxemia related to congenital malformations of the heart, no evidence was obtained of a correlation between the degree of hypoxemia or the extent of the polycythemia and the systemic blood flow. The circulatory response to exercise was characterized by a greater increase in the arteriovenous oxygen difference than in the systemic blood flow. A syncopal reaction in one patient was preceded by a greatly increased systemic blood flow and a small arteriovenous oxygen difference.

AMONG individuals with cardiac malformations which permit venous arterial shunts, the oxygen saturation of arterial blood varies widely, but when such persons are in a good state of nutrition it usually is more than 70 per cent. This article is concerned with the circulatory adjustments to hypoxemia related to congenital heart disease. Particular mention will be made of two possible mechanisms that may maintain the oxygen saturation of arterial blood above a certain critical level. The first possibility is an increase in systemic blood flow and the second is an increase in the oxygen capacity of the blood. Both these mechanisms would allow higher oxygen saturations of venous blood, the first by a decrease in the difference in oxygen content of arterial and venous blood through increased blood flow, the second by producing a smaller decrease in the oxygen saturation of the venous blood. The latter includes the assumption that the arteriovenous oxygen difference remains the same. If the shunted venous blood is highly saturated with oxygen, it is apparent that the shunt will cause less decrease in the oxygen saturation of the arterial blood than would an equal quantity of venous blood which is less well saturated with oxygen. The systemic flow values represent the systemic cardiac output, with both ventricles contributing to this output in the presence of an intracardiac venous shunt. The percentage of venous blood shunted tends to remain constant in some cases,[1] though in other cases, particularly during collapse reactions, the percentage of venous blood shunted (considered as a number of cubic centimeters of venous blood per 100 cc. of aortic flow) may be markedly increased. Further analysis of the factors responsible for the drop in arterial oxygen saturation with exercise constitutes the second purpose of this paper.

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## Methods

From the group of patients on whom venous catheterization of the heart has been performed in our laboratory, 20 subjects were selected who were in a good state of nutrition and who seemed to have accommodated themselves reasonably well to their intracardiac shunt and the consequent decreased tolerance to exercise. Individuals constantly unable to carry out mild activity were excluded as were those with extremely low arterial oxygen saturation. The majority of the patients were adults and none had shown any recent change in their compensation to their defect as judged by the history. None, however, could be said to have a normal tolerance to exercise.

The physiologic tests performed on each patient were in two parts, and a day or so intervened between the tests. The first was the exercise test in which the patient walked on a treadmill at 1.7 miles per hour, during which time the arterial oxygen saturation was measured by an ear oximeter[2] and was also determined at intervals by manometric analysis[3] of a sample of blood withdrawn with an indwelling arterial needle. Exercise was routinely continued for five minutes, unless the patient's tolerance to exercise did not permit him to continue as noted in table 1.

TABLE 1.—*Summary of Data in Twenty Cases*

| Case | Age (yr.) | Clinical Diagnosis | Tolerance of Exercise | Surface Area, (Sq. M.) | B.M.R. % | $O_2$ Uptake, (Ml. per Min. per Sq. M.) | RQ | Systemic Blood Flow, (Liters per Min. per Sq. M.) | $O_2$ Capacity (Vol. per 100 cc.) | Arterial $O_2$ Satuation (%) | | A-V Difference, (Vol. per 100 cc.) (Resting) | Pressure P.A. (mm. Hg) (Resting) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | At Rest | Drop on Exercise | | |
| 1 | 27 | Eisenmenger's complex | Fair | 1.80 | 0 | 138 | 0.79 | 2.4 | 23.4 | 90 | 17 | 5.7 | 112/55 |
| 2 | 24 | Eisenmenger's complex | Poor | 1.82 | +11* | 153 | 0.84 | 2.5 | 22.6 | 90 | 15 | 6.2 | |
| 3 | 25 | Eisenmenger's complex | Fair | 1.45 | +45 | 172 | 0.94 | 3.3 | 21.8 | 80 | 21 | 5.2 | 117/52 |
| 4** | 18 | Eisenmenger's complex (?) | Poor | 1.43 | +6* | 134 | 0.83 | 1.1 | 32.0 | 75 | 8** | 11.7 | |
| 5 | 26 | Eisenmenger's complex | Fair | 1.83 | +10 | 135 | 0.83 | 3.5 | 22.4 | 83 | 15 | 3.9 | 114/67 |
| 6† | 25 | Isolated dextrocardia; septal defect | Fair | 1.74 | +22 | 169 | 0.79 | 4.3 | 16.0 | 86 | 33† | 3.9 | |
| 7‡ | 16 | Isolated dextrocardia; septal defect | Fair | 1.32 | +17* | 182 | 0.82 | 3.8 | 23.0 | 77 | 8‡ | 4.8 | |
| 8 | 15 | Isolated levocardia; septal defect | Fair | 1.58 | +29 | 183 | 0.71 | 6.8 | 22.0 | 79 | 10 | 2.7 | |
| 9 | 11 | Eisenmenger's complex (?) | Good | 1.27 | +10* | 173 | 0.93 | 4.9 | 26.2 | 78 | 38 | 3.5 | |
| 10 | 31 | Atrial septal defect | Fair | 1.76 | +28* | 157 | 0.80 | 2.4 | 28.8 | 78 | 24 | 6.5 | |
| 11§ | 35 | Tricuspid atresia | Good | 1.68 | +23* | 168 | 0.67 | 2.5 | 33.7 | 80 | 33 | 6.7 | |
| 12 | 15 | Tricuspid atresia | Fair | 1.60 | +20 | 169 | 0.76 | 3.4 | 25.3 | 79 | 20 | 5.0 | |
| 13‖ | 16 | Pulmonary stenosis; atrial septal defect | Poor | 1.57 | +11 | 176 | 0.77 | 3.5 | 27.8 | 63 | ‖ | 5.0 | |
| 14 | 18 | Tetralogy of Fallot | Poor | 1.38 | +6 | 136 | 0.77 | 3.9 | 27.6 | 77 | 25 | 3.5 | 15/6 |
| 15 | 18 | Tetralogy of Fallot | Fair | 1.68 | +2 | 155 | 0.75 | 4.2 | 33.5 | 75 | 34 | 3.7 | |
| 16 | 8 | Tetralogy of Fallot | Poor | 0.97 | +10* | 200 | 0.73 | 6.9 | 26.2 | 78 | 30 | 2.9 | |
| 17§ | 34 | Tricuspid atresia | Good | 1.63 | +12 | 157 | 0.81 | 3.7 | 29.5 | 86 | 16 | 4.3 | |
| 18 | 48 | Ventricular septal defect | Fair | 1.73 | +26 | 163 | 0.78 | 2.5 | 25.4 | 95 | 11 | 6.5 | |
| 19 | 15 | Eisenmenger's complex | Fair | 1.41 | +3 | 165 | 0.78 | 2.9 | 30.6 | 79 | 29 | 5.7 | |
| 20† | 43 | Eisenmenger's complex | Poor | 1.79 | +47 | 193 | 0.80 | 4.7 | 15.2 | 68 | 33† | 4.1 | 132/44 |
| Average | 23.4 | | | | | | | 3.7 | 25.9 | 80.3 | | 5.1 | |

* Light breakfast.

** Patient unable to exercise more than two minutes.

† Recent pulmonary hemorrhages.

‡ Drop in saturation by standard oximeter only.

§ Some of the clinical and diagnostic features of Cases 11 and 17 have been discussed by Geraci, Dry, and Burchell (Atrial Septal Defect and Probable Tricuspid Atresia in Adults, Proc. Staff Meet., Mayo Clin. **23**: 510–516 Oct. 27] 1948.)

‖ Patient unable to carry out exercise in laboratory.

The second part of the investigation consisted of cardiac catheterization after the method of Cournand and Ranges[4] as modified by Wood and associates.[2] All the tests were performed in the morning and many of the patients had had a light breakfast approximately two hours previously. The breakfast was allowed on the thesis that true basal states could not be obtained in any instance and as the procedure was primarily for diagnostic purposes, the patient would be more comfortable during the procedure if he ate breakfast. The oxygen saturation of arterial blood was determined throughout the procedure by a modified ear oximeter[2, 5] and samples obtained from the catheter were assayed for their oxygen saturation by means of the whole blood oximeter.[6] These results were checked frequently against Van Slyke analyses.

Determinations of oxygen uptake were done by the collection and analysis of expired air in a metal gasometer and the metabolic rates were determined by the Mayo Foundation standards as discussed by Boothby, Berkson, and Dunn.[7] The period of collection of the expired air in the resting state varied between five and ten minutes.

In 4 patients (Cases 17 to 20) an exercise test was carried out while the tip of the cardiac catheter was in the right atrium and samples of blood were obtained simultaneously from the catheter and from an indwelling arterial needle (table 2). The oxygen uptake during exercise was determined by the collection of the expired air beginning after the first minute of exercise and continued for the length of the exercise as a rule, either as a single collection or two collections.

Approximately one-half of the patients had a ventricular septal defect and a large pulmonary artery, which is Eisenmenger's complex in general. It must be emphasized that the problem of obtaining samples of the blood representative of true mixed venous blood in the presence of intracardiac defects is a difficult one as interchamber mixing of blood may occur and samples from the superior and inferior venae cavae may show considerable difference (frequently 1 to 1.5 volume per 100 cc.) in their oxygen content. We attempted to minimize the difficulty by depending on the oxygen content of blood from the vena cava checking well with that of blood from the right atrium. Patients from whom adequate samples were not obtained were excluded from this series.

TABLE 2.—*Circulation Measurements at Rest and Exercise in Selected Patients*

| Case | Age (Yr.) | Diagnosis | Position | $O_2$ Uptake (Ml. per Sq. M. per Min.) | RQ | Systemic Blood Flow, (Liters per Sq. M. per Min.) | Arterial $O_2$ Saturation (per cent) | A–V $O_2$ Difference (Vol. per 100 cc.) | Resting $O_2$ Capacity (Vol. per 100 cc.) | Per cent Venous Blood Shunted |
|---|---|---|---|---|---|---|---|---|---|---|
| 17 | 34 | Tricuspid atresia | Supine | 157 | 0.81 | 3.7 | 86 | 4.3 | 29.5 | 46 |
| | | | Standing | 173 | 0.79 | 3.4 | 88 | 5.1 | | 40 |
| | | | Walking | 331 | 0.84 | 4.4 | 70 | 7.3 | | 52 |
| 18 | 48 | Ventricular septal defect | Supine | 163 | 0.78 | 2.5 | 95 | 6.5 | 25.4 | 10* |
| | | | Standing | 168 | 0.79 | 2.2 | 95 | 7.7 | | |
| | | | Walking | 395 | 0.81 | 3.4 | 85 | 11.6 | | 22 |
| 19 | 15 | Eisenmenger's complex | Supine | 165 | 0.78 | 2.9 | 79 | 5.7 | 30.6 | 46 |
| | | | Standing | | | | 77 | 6.0 | | 46 |
| | | | Walking | 372 | 0.94 | 3.8 | 48 | 9.8 | | 60 |
| 20 | 43 | Eisenmenger's complex | Supine | 193 | 0.80 | 4.7 | 68 | 4.1 | 15.2 | 52 |
| | | | Standing | 210 | 0.76 | 3.8 | 61 | 5.6 | | 51 |
| | | | Walking | 283 | 1.06 | 8.1 | 39 | 3.5 | | 73 |

* See text for discussion of validity of calculation.

## RESULTS

The results are summarized in table 1. The patients as a rule had elevated metabolic rates. All of them, however, when resting were quiet

during the collection of the expired air and showed no overt signs of marked apprehension, and most had normal respiratory quotients.

In some patients with congenital intracardiac venous shunts we have observed that the oxygen saturation of arterial blood drops with exercise to a level which is characteristic for the individual (fig. 1), and the level may not be changed by increment in the work, namely, by increasing the rate of walking from 1.7 to 2.2 miles per hour.

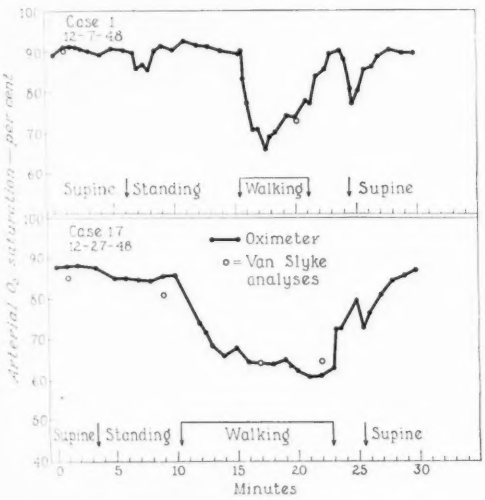


FIG. 1.—The effect of exercise on the oxygen saturation of arterial blood in 2 of our patients (Cases 1 and 17) as measured by a modified oximeter reading and arterial samples. In Case 1, improvement during exercise followed the initial drop while in Case 17 the arterial saturation was maintained at a low level during exercise. Both patients show a characteristic transient drop in the arterial oxygen saturation on changing to the supine position following their exercise. This is believed to be related to a rapid return to the heart, when the supine position is resumed, of the desaturated blood pooled in the legs during the periods of standing.

The average systemic blood flow measured as liters per minute per square meter of body surface was 3.7, with a range from 1.1 to 6.9. There was a trend for the flow to be greater in patients having the lower values for the oxygen capacity of the blood, but this was without statistical significance (correlation coefficient −0.34).

The arterial saturation of blood during resting showed no definite correlation with the oxygen capacity of the blood (correlation coefficient −0.13) or the resting systemic flow (correlation coefficient −0.24) in this group of patients.

The drop in oxygen saturation of arterial blood on exercise showed no definite correlation to the arterial oxygen saturation during rest, the systemic flow during rest, or the oxygen capacity of the blood. The correlation coefficients being −0.37, +0.30, and +0.06, respectively.

The change in systemic flow related to exercise of 4 patients is shown in figure 2. None of these 4 patients showed the common manifestations of heart failure, that is, systemic or pulmonary congestion. They were comfortable at rest and their hearts were not grossly enlarged. The 3 patients (Cases 17, 18, and 19) who completed the five-minute period of exercise (walking 1.7 miles per hour on the treadmill) did so without obvious distress and the circulatory response was characterized by widening of the arteriovenous oxygen difference with little increase in systemic flow. The patient (Case 20) who was unable to continue walking showed an opposite response. The data in Case 18 is graphically portrayed (fig. 3) and the plateau levels of oxyhemoglobin of both the arterial and mixed venous blood are to be noted. The patient may be said to have been in a steady physiologic state during the exercise period. In contrast, the results in Case 20 (fig. 4) show a progressive decrease in arterial saturation without evidence of equilibrium being established, and this was associated with progressive deterioration in the clinical state of the patient and finally with collapse.

## COMMENT

All of these patients had a varied degree of disability, and, though free of edema or dyspnea at rest, could be said to have inadequate circulation under conditions of exercise. The symptoms that appeared in some patients, either singly or together, were exhaustion, weakness, faintness or dyspnea.

The results of the metabolic rates were equivalent to those we could expect in a group

of normal subjects under resting but nonbasal conditions. These patients presented no evidence of reduced tissue metabolism such as has been claimed by Bing and co-workers[8] to occur in more severely hypoxic children with congenital heart disease. The results in our group are in accord with the observations of Houston and Riley[9] on individuals during acclimatization to low barometric pressure who showed no change in their oxygen consumption under conditions of rest and standard exercise at low pressure. Similar results were obtained by Douglas and co-workers,[10] on frequent studies of oxygen consumption performed under conditions of rest and during exercise before and after ascent to Pike's Peak. The figures for the oxygen uptake at near sea level and at altitude were remarkably uniform. Similar uniform results in the oxygen uptake in 2 subjects at low and high altitude were obtained by Grollman.[11]

The average systemic blood flow of our 20 patients was slightly above the average normal as reported by Stead and his co-workers[12];

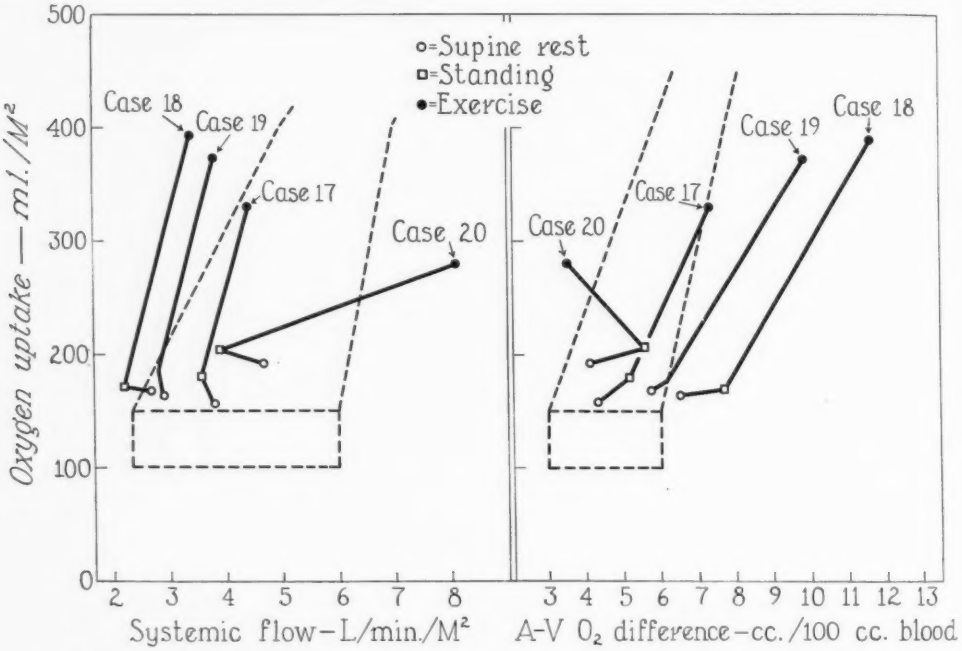


FIG. 2.—The effect of exercise on the systemic blood flow and oxygen consumption in 4 patients discussed in the text. The oxygen saturations of arterial blood in Case 17 dropped from 86 to 70 per cent on exercise; in Case 18 from 95 to 85 per cent; in Case 19 from 79 to 48 per cent and in Patient 20 from 61 to 39 per cent. In Case 20 a physiologic steady state was never present and exercise lasted only a minute and a half. The dotted lines represent the border of normal responses and were constructed by finding boundaries that would enclose the charted results obtained for 3 normal persons by Riley and his co-workers[24] and for 7 normal persons by Hickam and Cargill.[28] Subject 5 of the latter investigators was excluded as the results for this subject differed so radically from those of the other subjects.

the lowest and highest values are definitely outside the normal range. However, Stead and his associates found the average index to be 3.3 for the composed subject as compared to 5.5 for the anxious one. Bing and co-workers[8] likewise have found wide variation in the systemic flows of their cyanotic patients; the values in their cases, expressed as liters per minute per square meter of body surface, ranged from 0.90 to 11.40. In their group of 5 patients with the

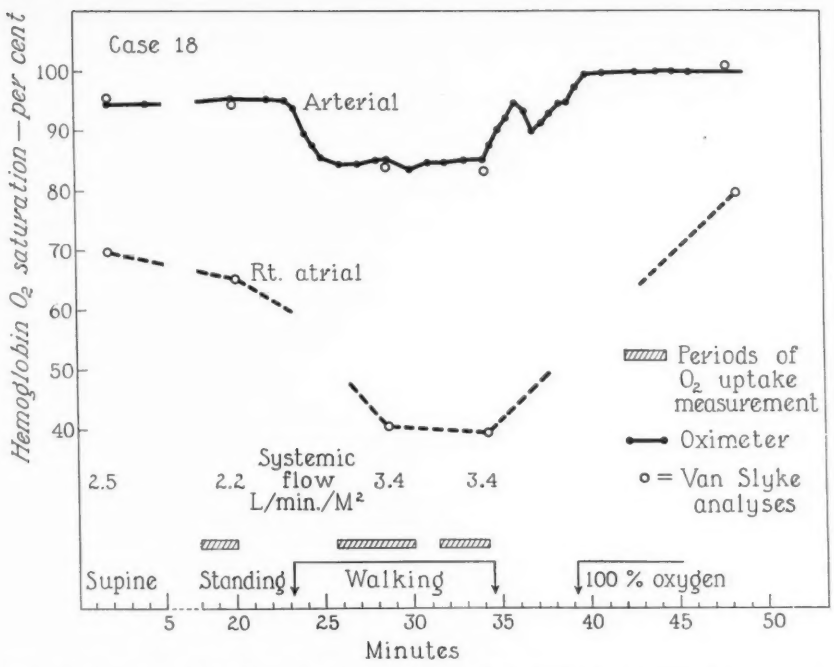


FIG. 3.—The effect of walking on the oxygen saturation of arterial and venous blood and the systemic blood flow in a patient with congenital heart disease (Case 18).

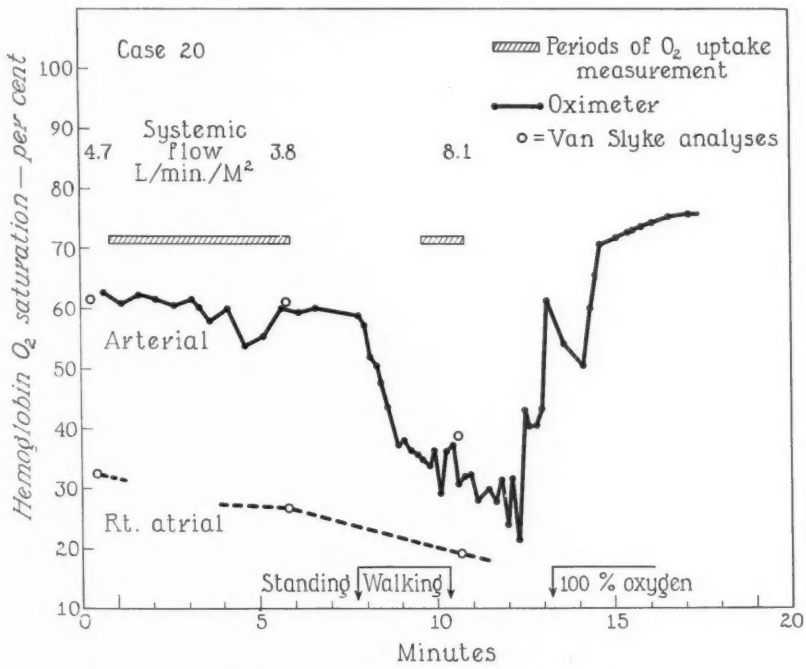


FIG. 4.—The effect of walking on the oxygen saturation of arterial and venous blood and systemic blood flow in a patient with congenital heart disease (Case 20).

Eisenmenger complex, Bing and his associates[13] found the systemic flow to be at low normal values (average 2.7).

The maintenance of a favorable minimal oxygen saturation of arterial blood in cases of pulmonary arteriovenous fistulas through an increased systemic blood flow was suggested as a possibility by Burchell and Clagett.[14] Actual determinations on this type of case are rare but the flow may be of normal value as in the case of Maier and associates[15] or increased as in the cases of Baer[16] and of Baker and Trounce.[17]

Extensive investigations have been carried out at high altitude concerning the effect of the hypoxemia on cardiac output. The fairly recent work of Asmussen and Consolazio[18] on Mount Evans is in general agreement with that of Grollman[11] on Pike's Peak in indicating that an increased circulation rate (increased systemic flow) occurred early in the acclimatization period. Grollman, from observations on hypoxia produced by mixtures of oxygen and nitrogen, concluded that the stimulus came at rather specific hypoxic levels, that is, when the oxygen in the inspired mixture dropped to 11.6 per cent. Such a stimulus threshold was supported by observations of Asmussen and Chiodi,[19] who found that the oxygen in the inspired air had to be low enough to reduce the arterial oxyhemoglobin to 70 to 80 per cent of normal in order to produce an increase in the cardiac output. In individuals acclimatized to low barometric pressure in a low pressure chamber for several days, Houston and Riley[9] found an increased cardiac output as one of the less significant compensatory mechanisms.

It is of interest that the 2 patients who had severe syncopal reactions on exercise showed a markedly different circulatory pattern prior to exercise. The one (Case 4) had an extremely low systemic flow (1.1 liters per minute per square meter), a big arteriovenous oxygen difference at rest, and prior to the faintness showed only a minor drop in arterial oxygen saturation on exercise. The other (Case 20) had a high systemic flow and a narrow arteriovenous oxygen difference at rest, and prior to faintness showed a marked drop in arterial oxygen saturation on exercise. In this latter case the respiratory quotient corresponding to oxygen consumption during the exercise was 1.06 (table 2). This is possibly related to the fact that the period of oxygen uptake was allowed to extend past the time that the patient was actually walking, though he was still standing in place on the treadmill. During the latter part of the collection period for expired air, excess carbon dioxide was being lost. However, the exercise alone might have been responsible.[10] The mixed venous and arterial oxygen saturations were reasonably steady during this period and the systemic flow value obtained probably has a validity in reflecting a high systemic flow. Such a presyncopal high systemic blood flow in a severely hypoxic condition would suggest a reaction analogous to that observed by Anderson and associates[20] in which high blood flows were obtained in muscle in the induced hypoxic state prior to syncope. In their subjects, bradycardia was a characteristic finding; in our patient, persistent tachycardia was recorded throughout the procedure by a cardiotachometer.

In the circulatory collapse in normal subjects associated with anxiety, observed by Hickam and associates,[21] the cardiac output either dropped slightly or remained the same and similar results were reported by Warren and colleagues.[22] The latter also mentioned the marked slowing of the pulse rate. Barcroft and his co-workers,[23] in studies on posthemorrhagic fainting, observed small decreases in the cardiac output inadequate to explain the fainting. None of these investigative groups stressed the technical difficulties, namely, obtaining a well-fitting mask or mouthpiece and an adequate period of a minute or more, that have been of concern to us in the measurement of the oxygen uptake in the subject bordering on a collapse state.

Extremely important in any consideration of hypoxemia is the possibility that this condition may be self-aggravating through increased pulmonary resistance to blood flow. Riley and associates[24] noted that those patients who had pulmonary disease and whose arterial oxyhemoglobin dropped significantly during exercise were the ones whose pulmonary arterial pressures were highest during exercise. These workers questioned whether the elevation of

pressure in the pulmonary artery might be related at least in part to the associated anoxia. They stated that such a possibility was given some general support from the observation of Morley and associates[25] that in normal subjects the pressure in the pulmonary arteries rose with the breathing of 10 per cent oxygen, and from the experiments of von Euler and Liljestrand[26] on cats in which there was a constant decrease in the pressure in the pulmonary artery on administration of 100 per cent oxygen and an increase on administration of 10 per cent oxygen in nitrogen. Von Euler and Liljestrand concluded from their experiments that the regulation of pulmonary blood flow was mainly mediated by local action of the blood and alveolar gases.

In a case of venous arterial shunt it might be assumed that an increase in pulmonary vascular resistance would cause an increase in the venous shunt and a further decrease in the percentage of arterial oxyhemoglobin. With the increased hypoxemia with exercise it is possible that a reciprocating aggravation of the hypoxic state might occur in which both factors, the hypoxemia and pulmonary resistance, might propagate each other. We have no observations which support such a thesis and have some observations in 3 cases in which such a phenomenon did not occur, the shunt remaining constant with exercise. Our calculations concerning the venous shunt in these patients when 10 to 14 per cent and 100 per cent oxygen were administered do not reveal uniform results. In one patient a decreased venous shunt on the administration of 100 per cent oxygen apparently occurred; in others, the shunt remained the same. One patient (Case 17) of this group has been studied at frequent intervals for two years. He has breathed 8 per cent oxygen for five to six minutes without distress on a number of occasions and has exercised for five minutes (walking 1.7 miles per hour on a treadmill) while breathing 12 per cent oxygen without discomfort. Case 19 is of particular interest in that the arterial oxygen saturation decreased with exercise through the range wherein one might expect, from the work on hypoxic states of normal persons, that the cardiac output might be stimulated. There seems no evidence of this having occurred (fig. 5). Patient 20 of the series was probably the most hypoxic patient and the percentage of venous blood shunted was unchanged by breathing 100 per cent oxygen, being calculated as 47 per cent. From these early observations, the conclusion seems probable that in patients who have congenital heart disease the total pulmonary vascular resistance bears no constant relationship to the degree of hypoxia—which may be related to a high fixed precapillary resistance in a pulmonary stenotic lesion, in pulmonary arteriolar sclerosis, or in the bronchial arteries.

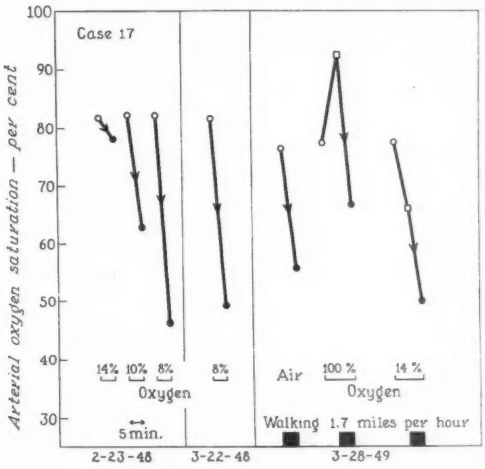


FIG. 5.—The effect of breathing various percentages of oxygen and of exercise on the oxygen saturation of arterial blood in a patient with congenital heart disease. The values charted represent those obtained by Van Slyke analyses of samples of blood drawn from the radial artery. The blood was taken with an indwelling arterial needle at the time when the ear oximeter showed that a plateau of arterial saturation had been established. This patient was also able to carry out the exercise test, walking 1.7 miles per hour on a power driven treadmill, breathing 12 per cent oxygen (Case 17).

For this heterogenous group of patients no conclusions can be drawn regarding the possible benefits of the polycythemia (or increased oxygen capacity of the blood). Long-continued intraindividual variations may have to be further studied in this regard. In the 2 individuals of this series with low hemoglobin (oxygen

capacities of 15 and 16 cc. per 100 cc.) related to recurring pulmonary hemorrhages, we could not be certain of a clinically suspected increased disability. The oxygen capacity of the blood in Patient 17 had been reduced from 34 to 21 volumes per 100 cc. by phlebotomies without reduction in tolerance to exercise but with a moderate, perhaps unrelated, decrease in arterial saturation during rest.[1] Likewise, due to variability between persons of this group, it would be unwise to draw any conclusions from the apparent possibility of slight inverse correlation between the oxygen capacity and the systemic blood flow.

It is of interest that Asmussen and Consolazio[18] stated that the drop in cardiac output after its initial rise at altitude was probably related to the development of polycythemia. As yet, evidence that polycythemia has a relationship to cardiac output is not convincing; for instance, all the early work as reviewed by Grollman[27] on polycythemia vera indicated that the cardiac output in this condition was normal.

The drop in oxygen saturation of arterial blood with standard exercise has shown no infallible correlation to the physiologic variables studied in this group nor with the general clinical impression of the individual's disability. However, as previously mentioned, the severely cyanotic children with extremely low oxygen saturation of arterial blood on exercise were not included.

The circulatory changes of 3 patients during exercise were similar to those of Hickam and Cargill's[28] patients with acquired heart disease who had congestive heart failure; that is, little increase in output with a large increase in the arteriovenous oxygen difference. It needs hardly be mentioned that even though the reaction is abnormal, it represents an increase in efficiency of the oxygen transport system. The fourth patient studied, already discussed in relation to the syncopal reaction, showed an increase in systemic blood flow with a narrow arteriovenous oxygen difference. In respect to the other 3 patients referred to, it is believed that they were in a relatively steady state during the exercise. In Case 18, serial samplings of expired air showed a close agreement in the oxygen uptake. It is of interest too that the increment in oxygen uptake of these 3 patients when walking at 1.7 miles per hour was in general agreement with the observations of Douglas and his associates,[10] who found the oxygen consumption was increased by a factor of 2.7 when subjects walked at 2 miles per hour. It may be noted that in Cases 18, 19, and 20 the percentage of venous blood shunted increased on exercise. The greatest increment in the shunt was in Case 20. The validity of the determinations of the percentage of venous blood shunted in these patients is dependent on the assumption that the pulmonary venous blood was normally saturated and remained so with exercise. The calculations were made after the method of Burchell and Wood.[1]

The arterial oxygen saturation under conditions of rest in Case 18 varied on two different days from 91 to 95 per cent. The calculation of any small shunt present is fraught with possible error. Breathing 100 per cent oxygen, this patient's arterial saturation was 100 per cent, and there were 1.6 cc. of excess oxygen in solution per 100 cc. of blood. At this time we could say no shunt was present. With exercise the arterial saturation abruptly decreased to 85 per cent and the calculated percentage of venous blood shunted was 22. It may be mentioned that a decrease of this magnitude in the oxygen saturation of arterial blood has been observed by us occasionally in patients with pulmonary congestion and with severe pulmonary disease, but this observation is opposite to the usual rule. In a previous publication, two of us reported the tendency of 2 patients, one of whom was Case 17, to maintain the same relative percentage of shunt under varying conditions. These further observations on additional patients indicate that an increase in the shunt may be an important contributing factor to the fall in arterial oxygen saturation under some conditions.

## Summary and Conclusions

In the group of patients with cyanotic congenital heart disease no correlations could be definitely established between the circulation rate (systemic flow) and the oxygen saturation or the oxygen capacity of arterial blood. The group was heterogenous in respect to age,

anatomic defect, and clinical disability. A threshold value below which the oxygen tension of arterial blood acted as a stimulus for an increase in systemic flow was not established in these cases.

The drop in arterial oxygen saturation on standard exercise showed no definite correlation to oxygen saturation of arterial blood or systemic flow during rest, to the oxygen capacity, or to the general clinical history.

It was apparent that polycythemia was not a uniformly necessary requirement for the well-being of the hypoxemic patient suffering from congenital heart disease of the cyanotic type.

The dynamics of the circulation of 3 patients completing a standard exercise test resembled that reported in the literature as characteristic of persons in heart failure, that is, the increased oxygen transport was related more to an increased arteriovenous difference than to increased cardiac output.

One individual, unable to continue exercise, whom we observed in the presyncopal state showed a great increase in the shunt of venous blood, a high systemic blood flow, tachycardia, and severe hypoxemia.

No evidence was obtained that increasing hypoxia caused increased pulmonary resistance in the special cases studied. This possibility has not been excluded in the other cases.

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# The Relationship between the Arterial Oxygen Saturation and the Cardiovascular Response to Induced Anoxemia in Normal Young Adults

*By* Raymond Penneys, M.D., and Caroline Bedell Thomas, M.D.

The induced anoxemia test of cardiovascular function has been standardized according to the *degree of anoxemia* rather than the oxygen concentration of the gas mixture administered. The cardiovascular response of normal subjects at 80, 75 and 70 per cent arterial oxygen saturation is described. The changes can be closely correlated with the degree of anoxemia, as measured by the oximeter.

AT THE present time the most widely used method of studying the effect of induced anoxemia on the cardiovascular system consists of giving the subjects low oxygen gas (usually 10 per cent) inhalation for approximately twenty minutes and making observations during this period. In previous communications[1–3] the variability of the degree of anoxemia, as measured by the blood arterial oxygen saturation, during inhalation of a gas of *fixed* low oxygen concentration was pointed out. The physiologic importance of standardizing the induced anoxemia test of cardiovascular function according to the level of the arterial oxygen saturation was discussed and a method of inducing and maintaining a constant degree of anoxemia by administering a gas of *variable* oxygen concentration was described. In one of these reports[1] the nature of the cardiovascular response of a small group of young men at levels of 85, 80, and 75 per cent arterial oxygen saturation was presented. It is the purpose of this report to give a detailed description and analysis of the effect of anoxemia upon the heart rate, blood pressure, and electrocardiogram at levels of 80, 75, and 70 per cent arterial saturation in a substantial number of normal young adults.

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## Method

Anoxemia was induced by the administration of mixtures of nitrogen and oxygen by means of a Heidbrink anesthesia machine. The arterial oxygen saturation was measured with the Millikan automatically-compensated oximeter. Details and modifications of the procedure have been reported elsewhere.[3]

Each subject rested on a bed in a quiet room until his or her blood pressure and pulse rate became stabilized. Electrocardiograms were made with a Cambridge electrocardiograph and standardized to give a 10-mm. deflection with 1 millivolt. In measuring the height of the RS-T segment, the P-Q or P-R segment was selected as the isoelectric line according to the method followed by Katz,[4] Malmström,[5] and others. Blood pressure was taken by the auscultatory method with a Tycos manometer; the heart rate was obtained from the electrocardiogram. The blood pressure, pulse rate, and electrocardiogram were taken before, during, and after the period of anoxemia.

A total of 76 normal persons was studied. Seventy-two were medical students and the remainder were laboratory assistants. All but 3 of the subjects were men. Seventy-three of the subjects were between 22 and 28 years of age; the other 3 subjects were 16, 17, and 34 years old. All subjects were of the white race and were free from any cardiovascular disease as far as could be determined by a preliminary examination, which included a detailed medical history, physical examination, and electrocardiogram.

Eighty-one tests were performed on the 76 subjects. In most instances the arterial oxygen saturation was lowered in a "step-wise" manner[3] so that a subject was studied at *more* than one level of saturation during the same test. The various readings (electrocardiogram, etc.) usually were taken at each level. If the saturation was maintained at only *one* level, readings were taken at the end of approximately ten and twenty minutes of anoxemia. The number of tests, according to the saturation at which

TABLE 1.—*Changes in the Electrocardiogram (RS-T Segment, T Wave, and Heart Rate) and Blood Pressure at 80, 75, and 70 per cent Arterial Oxygen Saturation*

| | | Changes in Arterial Oxygen Saturation (%) | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 95 (approx.) to | | | | | | | | | | | | (4) 80 to 75 | | | | (5) 75 to 70 | | | |
| | | (1) 80 | | | | (2) 75 | | | | (3) 70 | | | | | | | | | | | |
| | | N | M | R | σ | N | M | R | σ | N | M | R | σ | N | M | R | σ | N | M | R | σ |
| RS-T Dev. (mm.) | (I-IV incl.) | 64 | .60 | 0 to 1.5 | .52 | 67 | .73 | 0 to 2 | .61 | 28 | .86 | 0 to 2.5 | .71 | 41 | .32 | 0 to 1 | .31 | 24 | .31 | 0 to 1 | .38 |
| T Wave (mm.) | I | 64 | −.68 | −2 to +.5 | .51 | 67 | −.77 | −2.0 to +.9 | .51 | 28 | −1.19 | −2.7 to −.1 | .65 | 41 | (−.11) | −.8 to +.9 | .34 | 24 | −.45 | −1.8 to +.4 | .41 |
| | II | 64 | −1.04 | −3.7 to +.2 | .70 | 67 | −1.33 | −4.4 to +1.0 | 1.01 | 28 | −1.99 | −4.7 to −.5 | 1.03 | 41 | −.33 | −1.6 to +.8 | .57 | 24 | −.34 | −2.0 to +.6 | .54 |
| | III | 64 | −.37 | −1.5 to +.8 | .53 | 67 | −.66 | −2.6 to +.9 | .77 | 28 | −1.17 | −3.2 to 0 | .66 | 41 | −.20 | −1.4 to +.7 | .40 | 24 | −.35 | −1.0 to +.3 | .33 |
| | IV | 64 | −.75 | −2.9 to +3.3 | 1.24 | 67 | −.96 | −4.3 to +1.9 | 1.31 | 28 | −1.15 | −5.0 to +1.3 | 1.59 | 41 | −.52 | −2.7 to +2.2 | .92 | 24 | [−.21] | −1.7 to +1.0 | .67 |
| Heart Rate (per minute) | | 69 | +14.0 | +1 to +33 | 6.9 | 73 | +18.3 | 0 to +39 | 8.2 | 30 | +23.4 | +6 to +39 | 8.5 | 46 | 2.7 | −13 to +20 | 6.5 | 30 | +5.2 | −7 to +15 | 5.4 |
| Blood Pressure (mm. Hg.) | Syst. | 67 | +4.1 | −11 to +23 | 6.5 | 70 | +4.1 | −13 to +22 | 6.9 | 28 | +6.3 | −4 to +16 | 5.2 | 40 | [−.2] | −9 to +8 | 3.9 | 28 | [+1.0] | −12 to +10 | 4.3 |
| | Diast. | 67 | [+.9] | −12 to +13 | 5.2 | 70 | [+.5] | −12 to +12 | 5.6 | 28 | [−.1] | −12 to +10 | 5.5 | 40 | [−.4] | −9 to +6 | 3.6 | 28 | −1.9 | −8 to +9 | 3.9 |

(1) to (5) at top of columns indicate "column number" referred to in text. In (1), (2), and (3) changes from room air (approx. 95 per cent) to 80, 75, or 70 per cent are listed; in (4) changes from 80 to 75 per cent and in (5) 75 to 70 per cent are given.

N = number of observations. "N" for "heart rate" and "blood pressure" is slightly larger than that for "RS-T" and "T Wave" for the same group of subjects since occasionally electrocardiograms were not obtained either for technical reasons or because of abrupt termination of the test.

M = mean difference.

R = range of differences.

σ = standard deviation of the mean differences.

P = (probability that difference is due to chance) values are <0.005 in all instances except where ( ) are placed around "M" in which P is > 0.005 but < 0.05 or where [ ] is placed around "M" indicating P > 0.05.

RS-T Deviation = indicates total for all four leads regardless of direction of change from the control electrocardiogram.

readings were taken, are as follows: eleven at 80 per cent; thirty-two at 80 and 75 per cent; fourteen at 80, 75, and 70 per cent; eight at 75 per cent; sixteen at 75 and 70 per cent.

All subjects, therefore, were not studied at the same levels of anoxemia. To determine the effect of anoxemia at a particular level, such as 80 per cent saturation, all readings at 80 per cent were totalled and compared to the readings obtained on the *same* subjects during the control period. The *difference* was then expressed arithmetically. In columns 1, 2, and 3 of table 1, the differences between 80, 75, and 70 per cent saturation and the control readings on room air (before the anoxemia period) are presented. The differences in taking a group of subjects from 80 to 75 per cent are given in column 4 and from 75 to 70 per cent in column 5.

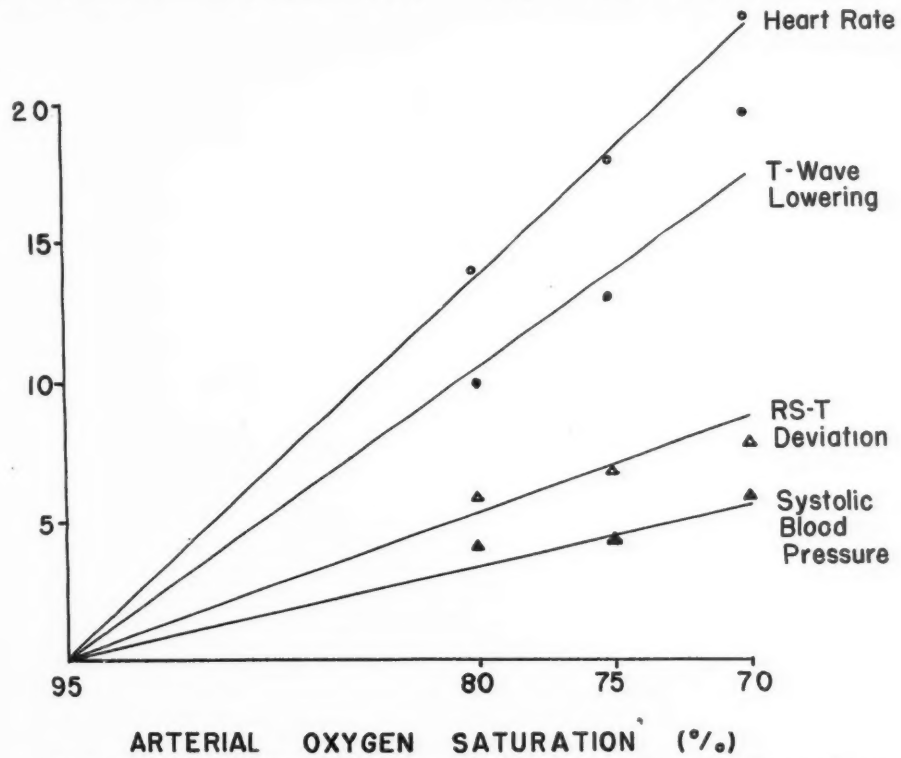


FIG. 1.—Changes with Progressive Lowering of the Arterial Oxygen Saturation. Heart rate change (○) in beats per minute; T-wave lowering (●) in Lead II in tenths of mm.; RS-T deviation (△) in Leads I–IV inclusive in tenths of mm.; systolic blood pressure (▲) in mm. Hg.

## OBSERVATIONS

### *Cardiovascular Response at 80, 75, and 70 per cent Arterial Oxygen Saturation*

The changes in heart rate, blood pressure, and electrocardiogram noted at these three levels are given in table 1. Graphic presentation shows that there is a progressive increase in certain values with lowering of the arterial oxygen saturation (fig. 1) which are consistent in the same individual at different levels of anoxemia (fig. 2). The nature and degree of these changes are described in detail below.

*Electrocardiographic Changes.* Changes in RS-T segment, T wave, P wave, and heart rhythm, and evidence of coronary disease were noted as follows:

RS-T Segment: The *total* RS-T deviation for Leads I to IV ($CF_4$), inclusive, increased slightly with progressive anoxemia. It did not exceed 2.5 mm. at 80, 75, and 70 per cent saturation in any individual. The distribution of RS-T changes for each lead at each level of arterial saturation is given in table 2. It can be seen that when a change did occur it usually was a depression of 0.5 mm. and was more com-

monly found in Lead II than in the other leads. A total of 37 out of the 76 subjects showed this type of change at one level or another.

Further evidence that the RS–T deviation increases with lowering of the arterial saturation is found in the increasing frequency of depression or elevation amounting to 1 mm., in any lead, in passing from 80 to 70 per cent saturation (table 2). Whereas, only 6 per cent of the subjects studied at 80 per cent showed that degree of deviation, 22 per cent of the subjects studied at 75 per cent and 43 per cent of the subjects studied at 70 per cent saturation showed such changes. In contrast, the percentage of subjects with *no* RS-T change in any lead decreased with lowering of the saturation. At 80 per cent saturation 38 per cent of the subjects showed no change, while at 75 per cent the percentage of subjects decreased to 28 per cent and at 70 per cent saturation to 25 per cent.

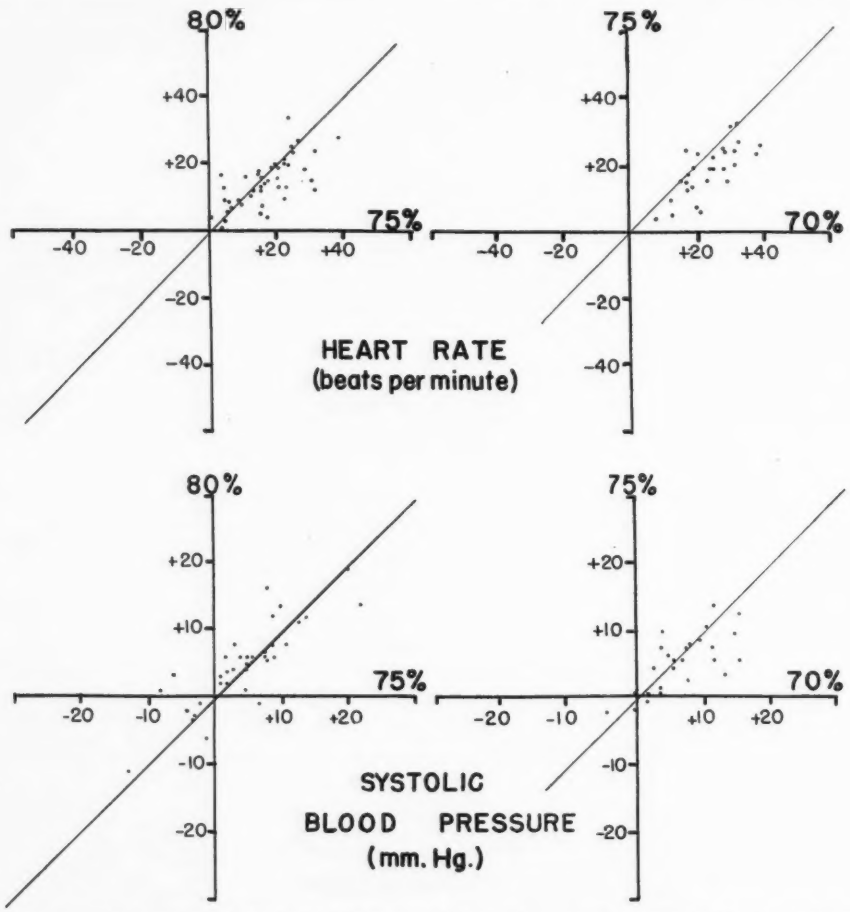


FIG. 2.—The Response of the Same Subjects to Different Degrees of Anoxemia. Each point represents comparison of changes noted in one subject at the arterial oxygen saturations indicated along the abscissa and ordinate. Reference lines are drawn at 45 degrees to indicate identical values at the two levels of arterial saturation. (Figure continued on facing page.)

T Wave: In practically every test the T wave was progressively lowered with diminishing arterial oxygen saturation. Statistical analysis of

the T-wave changes showed that the degree of lowering was closely correlated with the level of the arterial oxygen saturation. More striking evidence that the degree of T-wave lowering was related to the level of the arterial saturation was demonstrated in those tests where upright T waves became diphasic or inverted with progressive anoxemia (table 3). In all but one instance these directional changes of the T wave took place in Leads III or IV. The various types of T wave changes with progressive anoxemia are illustrated in figure 3.

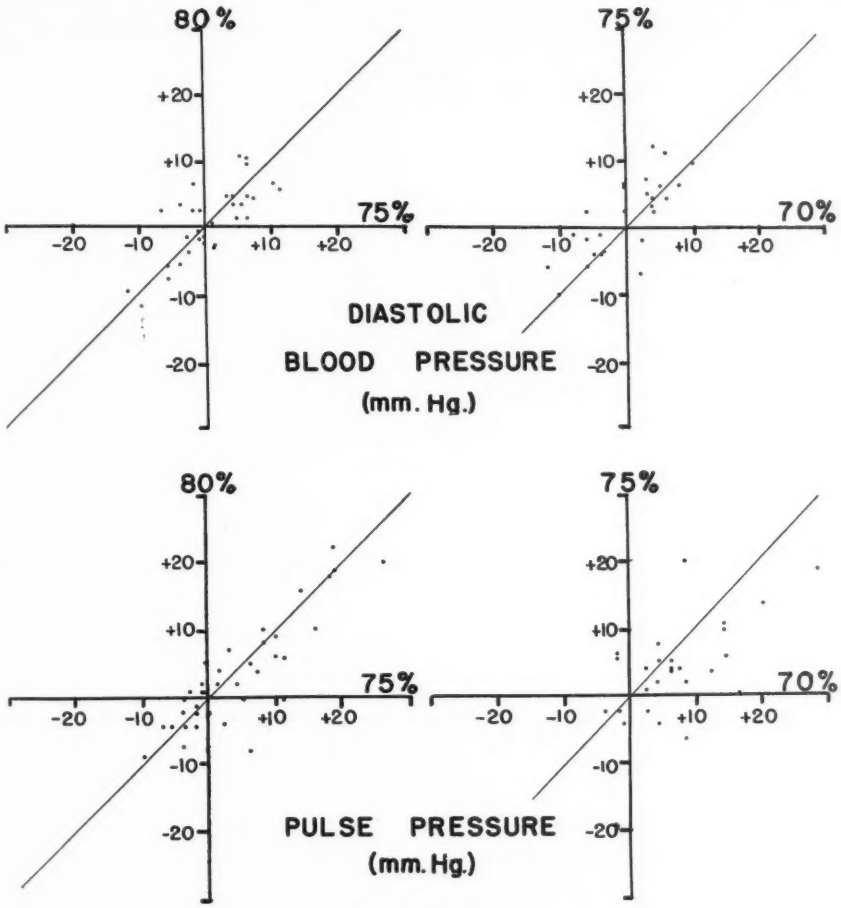


FIG. 2.—Cont'd.

P Wave: Ten subjects showed elevation of the P wave with anoxemia. The increase in height ranged from 0.5 to 3 mm. and was most pronounced in Leads II or III. The most striking example of elevation of the P wave with anoxemia is illustrated in figure 4. In this instance marked increase in $P_2$ and $P_3$ occurred upon decreasing the arterial oxygen to 75 per cent saturation, and there was no further increase at 70 per cent saturation. It may also be noted that $P_1$ decreased very slightly in amplitude, and the P wave in Lead $IV_F$ became inverted.

Rhythm: The heart rhythm remained regular during anoxemia; no transitory ectopic rhythms were noted. In two of three instances in which sinus arrhythmia was present during the control period, the rhythm became regular

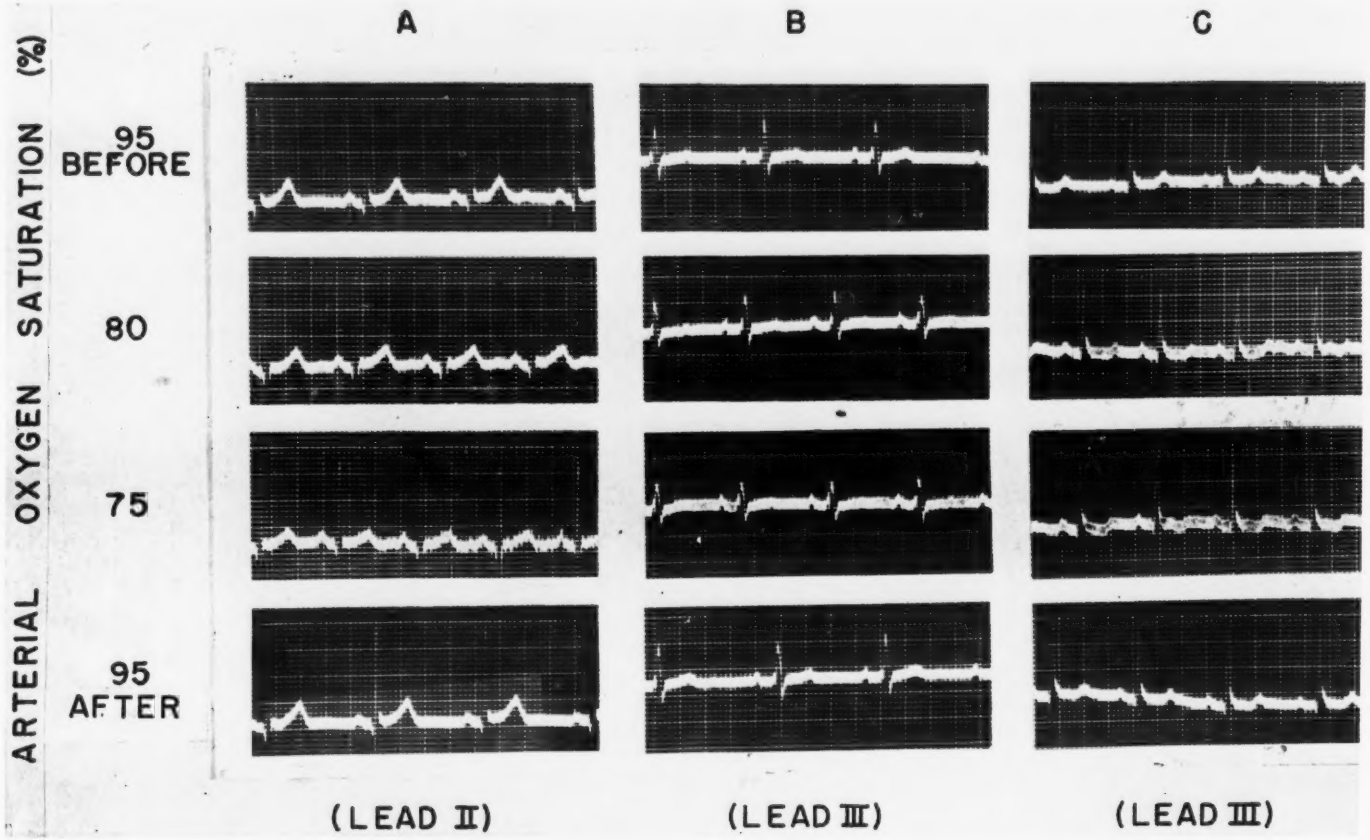


FIG. 3.—Different types of T-Wave Changes with Progressive Anoxemia. Subject A (49M26) shows *lowering* of the T wave, B (49M20) *flattening*, and C (48M56) *inversion*.

with anoxemia. In both tests this conversion of sinus arrhythmia into normal sinus rhythm was associated with a concomitant increase in the heart rate, amounting to 25 beats per minute.

TABLE 2.—*RS-T Deviations According to Lead of Electrocardiogram and Arterial Oxygen Saturation*

| | Changes in Arterial Oxygen Saturation (%) 95 (approx) to | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 80 | | | | 75 | | | | 70 | | | |
| RS-T Dev. (mm.) | I | II | III | IV | I | II | III | IV | I | II | III | IV |
| +1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| +0.5 | 2 | 0 | 1 | 6 | 3 | 2 | 3 | 6 | 0 | 0 | 0 | 1 |
| 0 | 50 | 41 | 52 | 39 | 58 | 38 | 45 | 44 | 26 | 15 | 18 | 18 |
| −0.5 | 12 | 21 | 11 | 19 | 5 | 19 | 17 | 13 | 2 | 6 | 7 | 6 |
| −1 | 0 | 2 | 1 | 0 | 1 | 8 | 2 | 4 | 0 | 7 | 3 | 2 |
| Total No. of Electrocardiograms | 64 | | | | 67 | | | | 28 | | | |

Numbers in blocks indicate number of electrocardiograms with indicated deviation. "Deviation" refers to arithmetic change from control value of RS-T segment on room air (before the period of anoxemia).

TABLE 3.—*Change in the Direction of the T Wave According to the Degree of Anoxemia*

| Subject's Study No. | Lead | Arterial Oxygen Saturation (%) | | | |
|---|---|---|---|---|---|
| | | 95 (approx) | 80 | 75 | 70 |
| 49M10 | III | upright | upright | inverted | — |
| | IV | upright | upright | diphasic | — |
| F.J. | IV | upright | — | diphasic | — |
| 48M56 | III | upright | diphasic | inverted | — |
| 48M33 | III | upright | diphasic | diphasic | — |
| 48W03 | III | upright | — | inverted | inverted |
| 48M81 | III | upright | upright | inverted | inverted |
| 51M28 | III | upright | — | — | inverted |
| 49M45 | III | diphasic | — | inverted | inverted |
| 49M19 | II | upright | — | inverted | inverted |
| | III | upright | — | inverted | inverted |
| 49W11 | III | upright | — | inverted | — |

— indicates no electrocardiogram made.

Evidence of Coronary Disease: No "positive"[6] electrocardiographic evidence for coronary disease were obtained at 80, 75, or 70 per cent arterial saturation.

*Circulatory Changes.* Changes in heart rate, blood pressure, and pulse quality were noted as follows:

Heart Rate: Increase in the heart rate with anoxemia occurred in almost every instance. The mean increase of the heart rate for the entire group of subjects was 14 beats per minute at 80 per cent saturation, 18 beats at 75 per cent, and 23 beats at 70 per cent saturation (table 1, columns 1–3). This progressive increase in heart rate with decreasing oxygen saturation is also demonstrated by the observations made in those subjects who were studied at more than one level of anoxemia (columns 4 and 5). It should be noted that while none of those tested had a slower heart rate during anoxemia than on room air, there were some individual decreases in rate when passing from 80 to 75 per cent and from 75 to 70 per cent, as is shown in figure 2.

Blood Pressure: The changes in blood pressure are also shown in table 1. There was an increase of 4 mm. in the mean systolic blood pressure at 80 and 75 per cent and of 6 mm. at 70 per cent over that obtained in the same individuals on room air (columns 1–3). Although these mean changes are small, they are statistically significant. The mean change in diastolic blood pressure at the same three levels, however, was slight (less than 1 mm.) and not statistically significant. These changes in the systolic and diastolic blood pressure resulted in a slight increase of the mean pulse pressure with anoxemia.

In contrast to these small changes of the mean blood pressure values, the individual responses to the same degree of anoxemia were often quite different, as is reflected in the ranges tabulated in table 1. Anoxemia produced a fall in systolic blood pressure in some subjects, and a rise in others; the diastolic pressures varied both concordantly and discordantly with the systolic readings. As a result, the pulse pressure changes were quite variable. The blood pressure changes were very consistent in the same subject at three different levels of anoxemia, however, regardless of the direction and degree of the change (fig. 2).

Pulse Quality: The quality of the pulse was kept under constant observation by palpation of the superficial temporal artery. In most

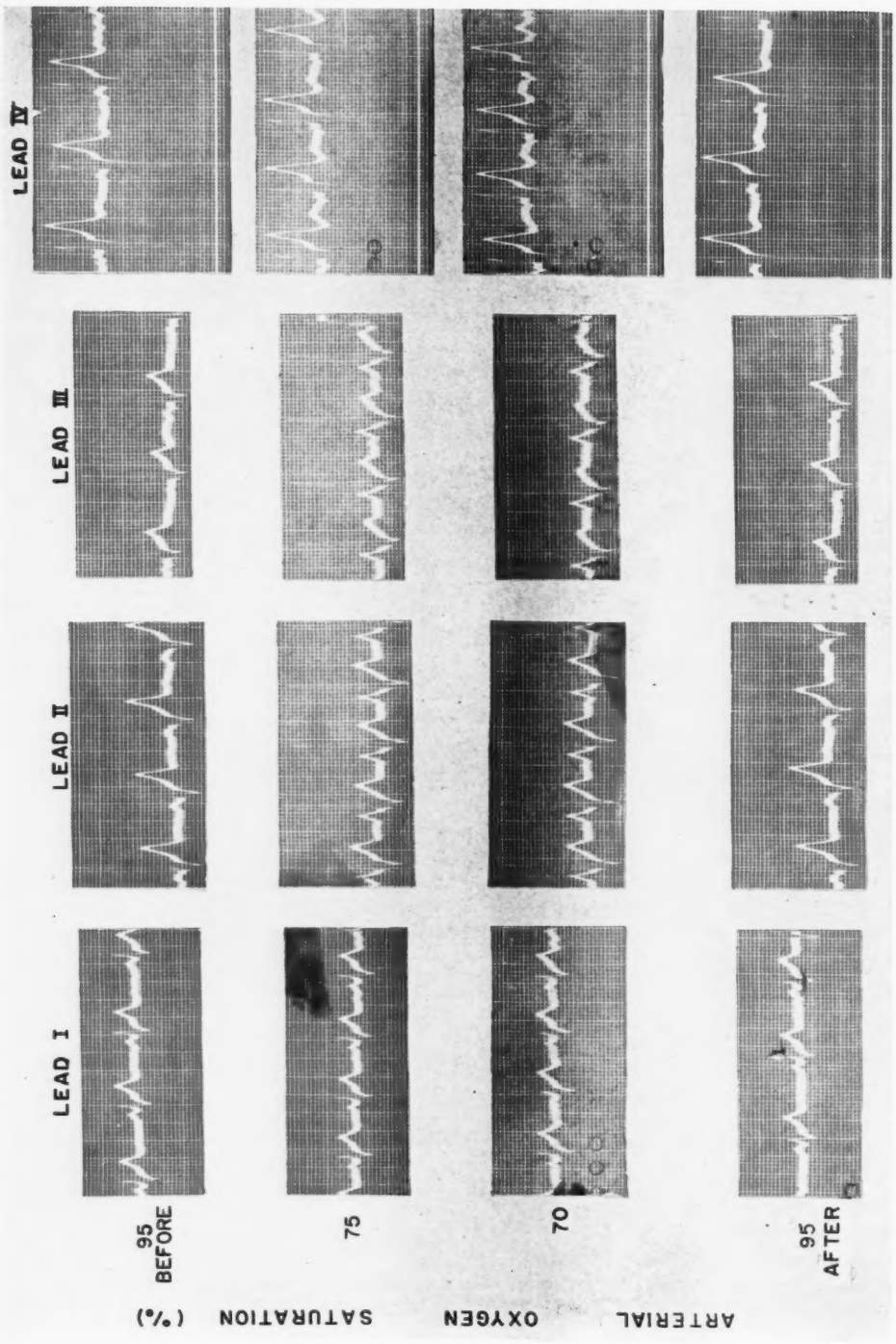


FIG. 4.—Elevation of the P Wave with Anoxemia (Subject 49M31). Records in Lead IV are mounted in their full width in order to include the entire QRS complex. 1 mv. = 10 mm.

persons there was an increase in the fullness and forcefulness of the pulse with the lowering of the arterial oxygen saturation. In a few instances, however, the pulse suddenly became weak with progressive anoxemia although there was no associated drop in the blood pressure. In one test this occurred at 80 per cent, in two at 70 per cent. When this happened the test was terminated because the change in pulse quality was interpreted as a sign of the individual's inability to adjust to anoxemia at that time.

*Relationship of the Heart Rate, Blood Pressure, and Electrocardiographic Changes to Each Other.* All the readings of the blood pressure, heart rate and electrocardiogram at *one* level of arterial saturation, 75 per cent, to which most of the subjects were taken, were tabulated and the following relationships studied:

Heart Rate Change and RS-T Depression: It has been reported that RS-T depression noted during anoxemia may be due to tachycardia alone, which is also produced by anoxemia.[7] Our data show that the degree of depression of the RS-T segment was not related to the degree of heart rate increase.

Heart Rate Change and T-wave Lowering: The degree of lowering of the T wave (in Lead II) was found to bear no statistical relationship to the degree of heart rate change. This observation, therefore, does not support the statement that *tachycardia* itself lowers the height of the T wave.[8]

Heart Rate Change and Pulse Pressure Change: The degree of heart rate change was found to bear no definite relationship, either direct or inverse, to the pulse pressure change at 75 per cent arterial saturation. Some subjects showed very little change in either the heart rate or the pulse pressure, while others showed marked changes in one or the other, or in both.

Degree of Cardiovascular Change at 75 per cent Arterial Saturation versus the Control Value (on room air): Larsen[9] has stated that the amount of T-wave lowering with anoxemia is proportionate to the height of the T wave on room air. Analysis of the degree of lowering of the T wave at 75 per cent saturation, in general, agreed with his statement. The degree of heart rate increase at 75 per cent saturation, on the other hand, bore no definite relationship to the absolute value of the heart rate in the control period. Also, the systolic blood pressure increase at 75 per cent saturation was not found to be related in any way to the absolute height of the systolic blood pressure on room air.

Combination of Unusual Responses: The tests of all subjects showing a marked response in any single feature (e.g., heart rate) were examined to determine whether these tests were unusual in other ways as well. All tests in which any of the following changes occurred were tabulated as "unusual": (1) heart rate increase greater than 25 beats per minute (5 subjects), (2) blood pressure change greater than 15 mm. systolic or 10 mm. diastolic (6 subjects), (3) RS-T deviation (Leads I–IV inclusive) 2 mm. or more (3 subjects), (4) T-wave inversion (in any lead) (7 subjects), (5) P-wave increase greater than 0.5 mm. (8 subjects). At 75 per cent arterial saturation, a total of twenty-nine unusual responses was shown by 22 different subjects. No consistent combination of unusual responses was noted in those 5 subjects with more than one such response.

*Duration of Anoxemia*

In the seventeen tests in which the arterial saturation was maintained at only one level (80 or 75 per cent) during the test, readings of the electrocardiogram and blood pressure were approximately the same at the end of ten and twenty minutes; no consistent difference could be found between the ten- and twenty-minute readings. Also, the pulse rate and quality, constantly observed throughout the test, usually showed no systematic change with increase in the duration of anoxemia, provided the level of arterial saturation was kept constant.

*Symptoms*

Only a few of the subjects could distinguish between breathing room air and the low oxygen gas regardless of the degree of anoxemia. This may have been related to the fact that induction to each level was gradual.

In two instances respiratory distress required early termination of the test. Both subjects manifested labored breathing and hyperventilation at the beginning of the test while still at a saturation of approximately 85 per cent.

Seven persons complained of mild frontal headache. This seemed definitely related to the degree of anoxemia. Five of these subjects noted the headache as soon as they reached 75 per cent arterial saturation and the other two on reaching the 70 per cent level. The headache was usually relieved by the inhalation of pure oxygen at the end of the test.

One subject, a medical student, who became excited and started to hyperventilate as soon as the nose clip and mouthpiece were in place, complained of "precordial pain radiating down the left arm" approximately one minute after he began to breathe the low oxygen gas, although the arterial oxygen saturation was still 95 per cent. No unusual changes occurred in the heart rate, blood pressure, or electrocardiogram. Prompt termination of the test resulted in immediate disappearance of the "pain."

## Discussion

The cardiovascular response of 76 normal young adults to the stress of anoxemia at 80, 75, and 70 per cent arterial saturation has been presented. These three standardized levels of physiologic stress were obtained by means of an oximeter-controlled method of inducing anoxemia which has been previously described.[1] The electrocardiogram, heart rate, and blood pressure showed increasing changes at successively lower levels of arterial saturation. These changes were quantitatively progressive, the response at 70 per cent saturation differing only in degree from that at 75 and 80 per cent. This indicates that at these levels of anoxemia, normal subjects can still compensate for the increasing stress by means of an increased physiologic response,[10] and are therefore still in the "pre-crisis" state of anoxemia. The absence of any *abrupt* change in the cardiovascular response as the arterial saturation was lowered to 70 per cent gives evidence that the "post-crisis" state of anoxemia, with impending collapse, was not reached in any of the 30 subjects carried to that level.

In general, the degree of cardiovascular response to induced anoxemia showed a close statistical correlation with the level of arterial oxygen saturation of the blood. From this it follows that any precise evaluation of cardiovascular function during anoxemia should preferably be based upon a form of anoxemia test in which the *level* of *arterial oxygen saturation*, rather than the oxygen concentration of the inspired gas, should be standardized, since there is no fixed relationship between the oxygen content of the inspired gas and the oxygen saturation of the blood.

The data on our 76 normal subjects gives information of direct clinical value concerning the present criteria for a "positive" reaction to the anoxemia test for coronary artery disease. The *maximal* electrocardiographic changes noted in our group of subjects at 80, 75, and 70 per cent arterial saturation do not overlap the criteria for a positive reaction to the test as set forth by Patterson, Clark, and Levy.[6] Using 10 per cent oxygen to induce anoxemia, these authors classify a reaction as positive when any one of the following changes is found: (1) The arithmetic sum of the RS-T deviations in all four leads (I–IVF inclusive) is greater by 3 mm. or more, than in the control record. (2) Partial or complete reversal of the direction of the T wave in Lead I, accompanied by an RS-T deviation of 1 mm., or more, in this lead. (3) Complete reversal of the direction of the T wave in Lead IVF, regardless of any associated RS-T deviation in this lead. Not only were none of these "positive" criteria found in the electrocardiographic records of our subjects at 80, 75, and 70 per cent arterial saturation, but between the upper limit of our normal range and the lower limit of their "positive" criteria there remains a definite small gap, into which records with the following characteristics would fall: (1) Partial or complete reversal of the direction of the T wave in Lead I in the absence of any RS-T deviation in this lead. (2). An RS-T deviation greater than 1 mm. in any lead.

The significance of such records is still uncertain; they have not been considered "positive" heretofore, yet they do not fall within the normal range in this present series. Until observations made on a larger number of normal subjects have conclusively demonstrated that the changes listed above actually do occur in normal individuals, it seems justified to regard them as probably abnormal, and therefore

a "doubtful positive" reaction to the electrocardiographic test for coronary artery disease.

Oximeter-controlled induced anoxemia should not only help to establish the electrocardiographic criteria for a positive reaction to the test, but should also help to evaluate the subject's symptomatic response to inhalation of the low oxygen gas. When "precordial pain radiating down the left arm" is associated with nearly normal arterial oxygen saturation, as occurred in one of our subjects, it seems unlikely that the symptoms could be directly attributable to anoxemia. Without the oximeter reading, however, the reaction to this test would have to be considered as "presumptively positive."

Finally, the oximeter-controlled method of producing standardized degrees of cardiovascular stress through the use of comparable levels of anoxemia provides us with an excellent means of studying the individual patterns of response. The gross differentiation between the various types of response to induced anoxemia in different subjects could be made at relatively high levels of arterial saturation. The responses of the same subject at subsequent lower levels of anoxemia were similar save for slight gradual intensification in some instances, indicating that these cardiovascular patterns are highly characteristic of the individual.

## Summary

1. By the use of oximeter-controlled induced anoxemia, the cardiovascular response of 76 normal young adults was studied at levels of 80, 75, and 70 per cent arterial oxygen saturation.

2. There was an increase in the response with progressive lowering of the saturation.

3. The degree of cardiovascular response was closely correlated with the level of the arterial saturation.

4. Maximal electrocardiographic changes observed in our group were smaller than the minimal criteria established by Patterson, Clark, and Levy for persons with coronary artery disease.

5. A possible intermediate zone of electrocardiographic changes indicating a "doubtful positive" reaction to the test was delineated.

6. The importance of knowing the arterial oxygen saturation in evaluating "presumptively" positive reactions to the test was pointed out.

7. The type of cardiovascular response of the same subject was similar at different levels of anoxemia.

8. The cardiovascular pattern of response to anoxemia varied considerably from subject to subject.

### Acknowledgments

We should like to express our appreciation to Dr. Ross L. Gauld for his advice and assistance in the analysis of the data and to Mr. Howard W. Kolscher for his expert technical assistance.

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# Correlation of the Oxygen Saturation of the Blood and Changes in the Electrocardiogram, Blood Pressure, and Heart Rate During the Anoxemia Test

## Observations on Normal Persons and Patients with Suspected and Manifest Coronary Heart Disease

*By* JAMES A. L. MATHERS, M.D., AND ROBERT L. LEVY, M.D.

During the performance of a series of anoxemia tests the oxygen saturation of the blood has been determined by means of the Millikan oximeter. The levels of hypoxemia induced have been correlated with various other factors. The results are considered with particular reference to a possible critical range, within which changes in the circulation occur.

THE ANOXEMIA test for coronary insufficiency, as proposed by Levy, Bruenn, and Russell[1] in 1939, has been subjected to thorough clinical trial by a number of observers.[2] If properly performed on suitable subjects it is without hazard and yields results which are of value in clinical diagnosis. It has also been employed to study indirectly, in man, the action of various drugs on the coronary circulation.[3, 4] The result is determined by the effect of anoxia on the form of the electrocardiogram; criteria for a positive reaction have been established[5] and widely used.

The range of optimal levels of anoxemia at which such electrocardiographic changes occur is not known although it has been shown that there is wide individual variation with respect to the degree of anoxemia obtained while breathing 10 per cent oxygen.[6] This depends, in large part, on the rate and, particularly, the depth of respiration during inhalation of the low oxygen mixture. The present study was designed to ascertain whether there is a critical level of anoxemia at which significant alterations in the electrocardiogram are induced. The relationship of varying degrees of anoxia to changes in heart rate and blood pressure was also noted.

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This work was carried out under a contract between the Army Research and Development Board, Office of the Surgeon General, and Columbia University.

### MATERIAL, PROCEDURE, AND METHODS

Observations were made in 97 individuals on whom 109 anoxemia tests were performed. The oxygen saturation was measured by the Millikan oximeter.[7] The tests were performed according to the method described by Levy and his associates.[1, 2a–c, 5] At the end of the period of induced anoxemia the subject inhaled 100 per cent oxygen for two minutes; the final electrocardiogram and reading of oxygen saturation were made after the patient had then breathed room air for seven or eight minutes. Oximeter readings and observations of heart rate and blood pressure were recorded at one-minute intervals throughout each period of study. The criteria for a positive reaction were those previously outlined.[5]

The 97 subjects included 45 with coronary sclerosis, ranging in age from 40 to 73 years; the average was 53 years. There were 14 in whom the diagnosis of coronary sclerosis was in doubt before and after the test; these patients ranged in age from 35 to 58 years, with an average of 46 years. In 38 individuals there was no evidence of cardiovascular disease; they are referred to as "normals." The range of age in this group was from 29 to 59 years; the average was 46 years.

The results of the oximeter readings and the observations on heart rate and blood pressure were submitted to statistical analysis.* Those tests which were carried to completion were compared with twenty-two which were terminated in less than twenty minutes because of pain. No essential difference appeared to exist between the completed and the incompleted tests for the duration of the observation. On this basis all the tests have been pooled for this period. In cases where repeat tests were available for the individual, only the first test has been included in the analysis.

* We are indebted to Dr. John W. Fertig and Miss Isabel McCaffrey of the Department of Biostatistics.

## Results

There were no significant differences in the average oximeter readings in the patients with coronary sclerosis, suspected coronary sclerosis, and in the normal subjects (table 1), so that for presentation all are considered as a single group (fig. 1).

Table 1.—*Average Oximeter Readings for the Various Groups during the Test*

| Classification | Room Air | 10 Per Cent Oxygen | | | | | 100 Per Cent Oxygen |
|---|---|---|---|---|---|---|---|
| | After 5 minutes | Start | 5 minutes | 10 minutes | 15 minutes | 20 minutes | 1 minute |
| Coronary Sclerosis | 95 | 95 | 79 | 74 | 72 | 71 | 97 |
| Suspected Coronary Sclerosis | 95 | 95 | 82 | 78 | 78 | 75 | 98 |
| Normals | 95 | 95 | 78 | 74 | 73 | 72 | 98 |
| All Individuals | 95 | 95 | 79 | 75 | 73 | 73 | 98 |

During the control period, while the patient was breathing room air through the apparatus, the oxygen saturation of the arterial blood remained fairly constant, averaging 95 per cent, with a range from 92 to 98 per cent. The fall in saturation when the mixture of 10 per cent oxygen and 90 per cent nitrogen was administered was most marked in the first five minutes, the average falling from 95 to 79 per cent. It was less marked in the second five minutes (from 79 to 75 per cent) and minimal in the final ten minutes (from 75 per cent at ten minutes to 73 per cent at fifteen and twenty minutes).

While these figures give the curve of the averages it is readily apparent from the graph (fig. 1) that there was a wide range of individual variability after the low oxygen mixture was inhaled. When 100 per cent oxygen was administered at the termination of the period, the saturation of the blood rapidly returned to an average figure of 98 per cent in about forty-five seconds. In a small number of cases the patient was changed directly from the 10 per cent oxygen mixture to room air, and in these instances the return to normal saturation was slightly slower, or there was a rapid return to a saturation of 86 to 90 per cent, with a subsequent slow rise to normal saturation. The average points on this curve and the great individual variation from the average were similar to those found by other workers whose method involved the use of an equivalent partial pressure of oxygen.[8–11]

The degree of unsaturation obtained in each case in all probability depends on the volume of gas inhaled by the individual and is a factor of the depth of respiration more than the rate. In those instances in which the patient was apprehensive of the procedure, hyperventilation was more apt to occur and the resultant degree of unsaturation was less marked. In this series, one individual hyperventilated to such a degree in the original test that the arterial saturation never fell below 90 per cent. When the test was repeated at a later date the patient had become accustomed to the procedure and more normal respiration prevailed. This resulted in an average curve of anoxemia which

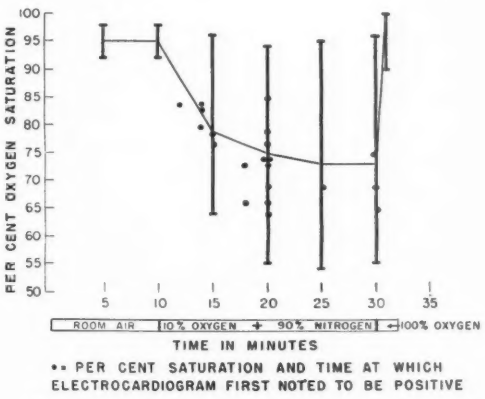


Fig. 1.—Curve of average oxygen saturation with range of individual variation, in relation to time at which electrocardiogram first showed significant changes.

of the School of Public Health, Columbia University, for their advice in making the statistical analyses.

showed 82 per cent at five minutes, 79 per cent at ten minutes, and 75 per cent at fifteen minutes. In both tests the electrocardiograms failed to reveal significant changes although the clinical diagnosis of coronary sclerosis had been made.

ration to a marked degree and with one deep inspiration often caused a change in saturation of 5 to 10 per cent. The second type was the well-conditioned, athletic person who compensated readily to the low oxygen mixture by a very slight increase in the respiratory rate and

TABLE 2.—*Average Heart Rate for the Various Groups during the Test*

| Classification | Room Air | 10 Per cent Oxygen | | | | |
|---|---|---|---|---|---|---|
| | After 5 minutes | Start | 5 minutes | 10 minutes | 15 minutes | 20 minutes |
| Coronary Sclerosis | | | | | | |
| Positive Test | 80 | 82 | 97 | 102 | 101 | 104 |
| Negative Test | 67 | 69 | 78 | 82 | 83 | 82 |
| Suspected Coronary Sclerosis | 74 | 75 | 84 | 86 | 86 | 88 |
| Normals | 76 | 76 | 89 | 91 | 92 | 91 |

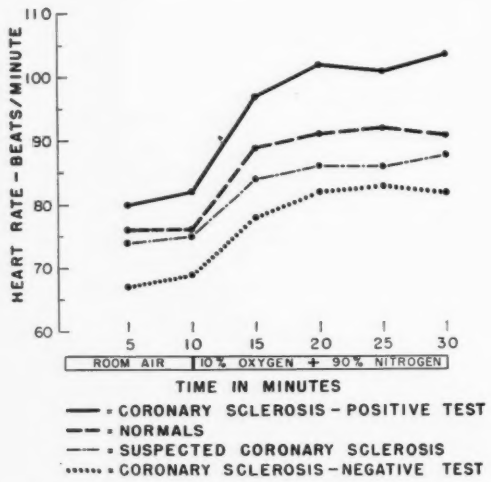


FIG. 2.—Curve of average heart rate during anoxia in various clinical groups.

In the total series, 16 individuals had an oxygen saturation curve which remained above 80 per cent in the original test. In 3 of these the reaction was positive within the first ten minutes, with the oxygen saturation at the time ranging from 83 to 85 per cent. In two types of patient a high degree of saturation was observed. The first was the apprehensive individual who obviously hyperventilated even during the control period and in whom the level never fell below 88 to 93 per cent. This type of patient increased both depth and rate of respiration a barely noticeable increase in the depth of respiration. The form of the curve of oxygen saturation was similar in character to the average but was maintained at a higher level, the lowest point reached being about 85 per cent.

In 4 individuals a drop in saturation to levels ranging from 55 to 60 per cent was obtained; of these 2 were normal subjects, one had coronary sclerosis, and in one the diagnosis of coronary sclerosis was suspected. In all 4 the respiration was slow and shallow throughout the test. The drop in saturation was rapid and associated with a definite increase in the heart rate of 20 to 40 beats per minute. None of these individuals experienced unpleasant symptoms or disturbing signs at this low degree of arterial oxygen saturation.

The average response of the heart rate is similar in the four groups (table 2 and fig. 2), namely, coronary sclerosis with a positive reaction to the test, coronary sclerosis with a negative reaction, suspected coronary sclerosis, and normal. Although the curves are similar, the average heart rate for the coronary sclerosis group with a positive reaction stays at a higher level throughout the test than for the coronary sclerosis group with a negative reaction. The curves for the suspected coronary and normal groups fall between the first two. The heart rate curve obtained is the inverse of that of the oxygen saturation. As the saturation of

the blood diminishes the heart rate increases; the rate and degree of increase are related to the rate and degree of fall in the arterial oxygen saturation. The average rise for all the cases studied as a single group was 12 beats per minute in the first five minutes with only a slight additional increase in the last fifteen minutes of the test. If the patient experienced pain in the chest there was usually an associated increase in the heart rate over that which was in whom the systolic blood pressure may increase 10 to 15 mm. Hg at the time of the pain.

Observations on the degree of anoxemia and the changes in the electrocardiogram in the individuals with coronary sclerosis have been analyzed in an attempt to determine four points: (1) the optimal level of anoxemia which one should attempt to attain in order to decrease the number of false negative results; (2) the time at which significant changes occur

TABLE 3.—*Average Systolic Blood Pressure for the Various Groups during the Test*

| Classification | Room Air | 10 Per Cent Oxygen | | | | |
|---|---|---|---|---|---|---|
| | After 5 minutes | Start | 5 minutes | 10 minutes | 15 minutes | 20 minutes |
| Coronary Sclerosis | | | | | | |
| Positive Test | 147 | 148 | 152 | 148 | 148 | 143 |
| Negative Test | 129 | 127 | 130 | 129 | 132 | 129 |
| Suspected Coronary Sclerosis | 139 | 139 | 143 | 143 | 138 | 140 |
| Normals | 130 | 129 | 135 | 137 | 136 | 135 |

TABLE 4.—*Average Diastolic Blood Pressure for the Various Groups during the Test*

| Classification | Room Air | 10 Per Cent Oxygen | | | | |
|---|---|---|---|---|---|---|
| | After 5 minutes | Start | 5 minutes | 10 minutes | 15 minutes | 20 minutes |
| Coronary Sclerosis | | | | | | |
| Positive Test | 84 | 84 | 89 | 85 | 84 | 83 |
| Negative Test | 79 | 78 | 80 | 79 | 79 | 79 |
| Suspected Coronary Sclerosis | 86 | 86 | 87 | 83 | 82 | 82 |
| Normals | 81 | 81 | 83 | 82 | 81 | 78 |

related to the degree of anoxia. In no instances were any abnormal cardiac rhythms encountered.

The average systolic (table 3) and diastolic (table 4) blood pressure curves for the four groups are essentially horizontal, showing little or no change as the test proceeds. The systolic pressure of the coronary sclerosis group with positive reaction shows a higher level throughout than those with a negative reaction. The normal individuals have about the same level as the group with coronary sclerosis with a negative reaction and those with suspected coronary sclerosis, and are intermediate between the positive and negative groups. Although there is no change in average blood pressure as the test proceeds, there are some individuals who experience pain during the test in the electrocardiogram; (3) the number of individuals who are able to complete the twenty-minute test; and (4) the value of the final ten minutes of the test (table 5).

As had been expected there was a wide range of saturation (63 to 84 per cent) at which the reaction was first noted to be positive, and no optimal point of saturation could be defined. The positive reactions in which the patient experienced pain during the first ten minutes were positive at a higher degree of oxygen saturation than in complete tests in which a positive result was obtained in the final ten minutes. This is in agreement with the oxygen saturation curve presented earlier and is a factor of the time at which the test was discontinued because of pain. It also indicates a greater degree of coronary insufficiency in those individuals in whom

it was necessary to terminate the test because of pain. In the series of 45 patients with coronary sclerosis, 17 showed a positive reaction within the first ten minutes; 6 of these occurred in five minutes or less. Of these, 13 experienced pain, so that the test had to be discontinued. Four patients had a complete test with the electrocardiogram showing a positive result in the final ten minutes, but without the occurrence of pain. While there were 24 subjects in whom the reaction to the test was negative, in 9 of these pain was experienced, so that the test had to be discontinued before the end of the standard twenty-minute period.

TABLE 5.—*Result of Test in Forty-five Patients with Coronary Sclerosis*

| Result | No. of Patients |
|---|---|
| Complete test—negative reaction | 15 |
| Incomplete test—negative reaction | 9 |
| Test discontinued (time in minutes): 5, 5, 5, 7, 9, 10, 14, 15, 15 | |
| Complete test—positive reaction | 8 |
| First noted positive (time in minutes): 10, 10, 10, 10, 15, 20, 20, 20 | |
| Incomplete test—positive reaction | 13 |
| First noted positive (time in minutes: 2, 3, 4, 4, 5, 5, 8, 9, 10, 10, 10, 10, 10 | |
| Test discontinued (time in minutes): 2, 3, 4, 4, 5, 5, 8, 9, 10, 10, 10, 13, 15 | |

It is apparent in table 5 that 23 subjects (51 per cent) were able to complete the twenty-minute test. If the test had been terminated at ten minutes, 32 of the 45 (or 71 per cent) would have been able to complete it. Although only 51 per cent completed the twenty-minute test, the outcome is unknown in only those 9 who still showed a negative result when the test was discontinued before the end of the twenty minutes. So, for 36 of the 45 subjects (80 per cent) the outcome in terms of a complete, or at least a positive, reaction was known. At ten minutes the comparable figure is somewhat larger, namely 89 per cent. Against the advantage of running the test for only ten minutes in order to reduce the number of tests not completed must be balanced the disadvantage of failing to detect as positive those in which diagnostic changes in the electrocardiogram occur after ten minutes. In this series there are 4 such individuals. We may speak of the "yield" of the test in picking up positives as 17 out of 45, or 38 per cent, by ten minutes, and 47 per cent by twenty minutes.

It is thus readily seen that the majority of the changes in the electrocardiogram occur early in the test during the period of most rapid fall in oxygen saturation and before compensatory mechanisms, which level off the curve, become operative. Nevertheless, changes do occur in the last half of the test, especially in the final five minutes, so that it appears worth while to continue the period of anoxemia for the full twenty minutes. In the individuals who show a positive result and experience pain, it is usually necessary to terminate the test, because of discomfort, in the course of the first ten minutes.

## COMMENT

It was suggested by Houston[8] and by Dripps and Comroe[9] that clinical applications of induced anoxia should be based upon arterial oxygen saturation or arterial oxygen tension attained rather than upon a specific percentage of inspired oxygen. Penneys and Thomas[12] carried out studies at three fixed levels, 85 per cent, 80 per cent, and 75 per cent. By using this maneuver in performing the anoxemia test, it was thought that a sufficient degree of anoxia would be assured to decrease the number of negative reactions in patients with mild degrees of coronary insufficiency. At the same time, according to these authors, it would lessen the number of so-called false positives which might result from higher grades of anoxia and would tend to prevent unpleasant reactions in the patient.

We have not been impressed, in the routine use of the test, by the frequent occurrence of false positives; in fact, a follow-up study of 150 patients in whom the test was performed during a ten-year period has not revealed any instance in which a positive reaction occurred in a patient subsequently found to be free of coronary heart disease.[13] By observing the precautions repeatedly outlined dangerous reactions can be entirely avoided and unpleasant symptoms largely eliminated.

It seems doubtful whether such a procedure would increase the incidence of positive reactions in patients in whom the degree of coronary insufficiency is relatively slight. In the apprehensive individual it would produce a greater sense of suffocation and could well result in a more marked degree of hyperventilation. Adequate control of the saturation at the desired level then would be practically impossible; frequent fine adjustments of the nitrogen flow are necessary in any case.[12] Varying the oxygen content of the inspired gas mixture might prove to be of some value in certain well conditioned subjects; in the routine use of the test, however, few of these are encountered.

Three of our 16 patients who hyperventilated showed an oxygen saturation curve which remained throughout above 80 per cent. The reaction was negative and was repeated on another day. A more normal type of respiratory response resulted in an oxygen curve at a lower level but the result was again negative.

## Summary and Conclusions

1. In a group of 97 individuals, including normal persons and patients with manifest and suspected coronary disease, 109 anoxemia tests were performed in the standard manner. Oximeter readings, observations of heart rate and blood pressure, and the usual series of electrocardiograms were made.

2. The level of anoxemia induced varied widely in the individual and in different individuals. No optimal range of oxygen saturation could be defined which caused electrocardiographic changes characteristic of a positive reaction to the test. The determining factor appeared to be the degree of impairment in the functional capacity of the coronary circulation.

3. The heart rate rose in response to anoxemia. The curve was the inverse of that for the oximeter readings.

4. The blood pressure failed to show any significant increase or decrease during anoxemia.

5. Changes in the form of the electrocardiogram occurred over a wide range of levels of anoxemia. The highest percentage of positive results was obtained during the first ten minutes of the test but a significant percentage was observed also during the final ten minutes. For this reason, unless the patient experiences pain or other discomfort, it is desirable to continue the period of anoxemia for the full twenty minutes.

6. Lowering the oxygen saturation in the apprehensive subject to a level below that which the body attempts to maintain may produce unpleasant reactions and is unlikely to increase significantly the number of positive results.

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# Peripheral Circulatory Changes as Criteria for Hemorrhagic Shock Therapy

*By* B. W. Zweifach, Ph.D.

This study of hemorrhagic shock syndrome in dogs evaluates commonly used therapeutic procedures on the basis of ability to correct specific vascular decompensatory episodes associated with progressive refractoriness to blood transfusion. Using specific criteria (vasomotion, responsiveness to vasoconstrictor stimuli, tone of arterioles and venules and capillary blood flow), it was found that pressor drugs improved blood pressure only at the expense of peripheral circulation. However, drugs such as angiotonin and especially pitressin, when added to the transfusion medium in subpressor concentrations sufficient to produce only a tonic narrowing of the terminal arterioles, brought sustained improvement in blood flow through the omental vessels. That the prognosis for successful treatment of the circulatory collapse closely parallels the sequential changes which occur in the terminal vascular bed, adds further significance to the probable causal relationship between the observed vascular derangements and the ultimate collapse of the peripheral circulation.

EXTENSIVE blood transfusion is at present the sole measure of proved value for preventing and counteracting the development of profound shock following massive hemorrhage or trauma.[1] However, when the shock is prolonged the condition becomes increasingly refractory to blood replacement therapy. Such a syndrome can be produced regularly in dogs, where graded hemorrhage leads to a condition in which the animal can no longer gain recovery by reinfusion of the blood withdrawn—the so-called "irreversible" stage of shock. Our microscopic studies of the circulation in the omentum of dogs has indicated that the downward course of the syndrome is related to a number of sustaining or perpetuating factors, other than fluid loss, which are of paramount importance in the development of the "irreversible" condition. A primary defect would appear to be the deterioration of specific vasomotor reactions concerned with the regulation of peripheral blood flow.[2] The establishment of these well defined reactions made it possible to use them as physiologic indices of the course of the syndrome and thereby offered a means for comparing the effectiveness of various therapeutic measures. Furthermore, the nature of the vascular derangement served as a guide for selecting agents which might contribute to the eventual recovery of the animal.

In our previous studies on the omental circulation an essential feature for recovery from shock was found to be an adequate improvement of the peripheral blood flow which was accompanied by, and appeared to depend upon, a sustained improvement in specific functional attributes of the peripheral vessels. It is the purpose of this study to compare the effectiveness of various therapeutic measures during the "irreversible" stage of hemorrhagic shock on the basis of their ability to correct the observed vascular dysfunction. No experiments were made to determine the long-range value of the measures employed, the end result looked for being a sustained improvement of the functional activity of the peripheral blood vessels for at least four to six hours, when the animals were sacrificed.

In the present paper two sets of experiments are described. The first deals with the relative effectiveness of blood and of several blood substitutes in restoring the deranged peripheral circulation. The restorative action of the fluids was found to differ according to the stage of the shock syndrome during which they were

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administered. Emphasis was placed on the stage when infusion of whole blood was no longer restorative but, on the contrary, accentuated the developing atony of the peripheral blood vessels by unduly dilating them.

The second set of experiments deals with the effects of various pressor and vasotonic agents, injected per se or used to fortify the whole blood infusion. The agents were selected for their possible counteracting effects on the deranged peripheral circulation at the time when fluid infusion alone was inadequate.

In most of the studies in the literature, the stage at which the animals become unresponsive to replacement of the blood volume deficiency has been determined only after the blood lost has been replaced.[3] The problem to be solved, however, is not irreversibility per se, as defined by the failure to respond to whole blood, but an analysis of the factors leading to such a condition. This makes the use of other, more physiologic, end points justifiable and even preferable to the more drastic procedure of allowing the animal to go into circulatory collapse twice before instituting therapy. When the syndrome has taken an unfavorable course and vascular and tissue metabolic deterioration has been initiated, time becomes a critical factor. The more prolonged the syndrome, the more likely is cellular damage to occur in organs which are sensitive to the effects of a stagnant anoxia. Blood replacement alone at this stage of the shock syndrome serves to accentuate further the developing functional derangement of the peripheral vascular system. This could be avoided by using as a criterion of the course of the syndrome the characteristic vascular changes, as observed through the microscope.

In order to permit a more direct comparison of the present experiments with similar work in other laboratories, a statistically significant number of experiments using the conventional blood-replacement end point were also carried out.

## Material and Methods

The present report includes observations on the effectiveness of various therapeutic measures following the induction of hemorrhagic shock in 126 dogs anesthetized with pentobarbital sodium (30 mg. per kilogram of body weight) or morphine sulfate (2 to 12 mg./Kg.). The dogs were bled according to Wiggers' method of removing blood at intervals, in decreasing amounts, until the blood pressure was brought to, and kept for a protracted period at, hypotensive levels. The routine procedure was to maintain a moderate hypotension of 60 to 50 mm. Hg for two to four hours and to follow this by a drastic hypotension of 40 to 35 mm. Hg, or below, for an additional one to two hours. The blood withdrawn was citrated (final concentration of 0.2 per cent), chilled, and reinjected via the femoral or jugular vein at a designated point in the experiment. Microscopic observations of the terminal ramifications of the peripheral vascular system were carried out on the exteriorized omentum of the dog according to the procedure previously described.[4] Essentially this involved maintaining the exposed portion of the omentum both warm and moist by irrigation with a Ringer gelatin solution kept rigidly at body temperature.

In tissues such as the omentum, possessing alternating periods of greater and lesser blood supply, the capillary bed consists of definitely organized units of structure and function. Particular attention was paid to the centrally located metarterioles and their precapillary branches. The following vascular criteria were selected as reflecting the functional state of the capillary bed.

1. *Vasomotion.* Variations in capillary flow are occasioned by periodic caliber changes, constrictor and dilator phases, of the metarterioles and precapillaries. During the constrictor phase only the precapillaries become completely occluded, and the circulation is restricted to the preferential channels leading from arteriole to venule. During the dilator phase the precapillaries are open and the majority of the capillaries become flushed with blood. This intermittent activity of the metarterioles and precapillaries has been termed *vasomotion.* Under normal conditions it is an integral part of the homeostatic mechanism which ensures a supply of blood commensurate with the needs of the tissue.

2. *Tone of Arterioles and Venules.* Normally these vessels are maintained in a partially contracted state. By loss of tone is meant an undue dilatation of vessel lumina. It is also indicated by an excessive distention of the vessels following the intravenous administration of fluids.

3. *Responsiveness to Epinephrine.* Another feature of importance in the adjustment of the peripheral circulation is the occurrence of variations in the responsiveness of its muscular vessels to physiologic stimuli, such as epinephrine. This was ascertained by determining the minimal amount of epinephrine which, on topical application, produced a partial narrowing of the arterioles and precapillaries sufficient to slow markedly the flow of blood through the capillary vessels. The precise amount of epinephrine required to bring about a similar vasoconstriction was determined at regular intervals.

4. *Rate of Flow.* The rate and extent of the capillary circulation, especially that on the venous side, is an excellent indication of the efficiency with which peripheral circulatory adjustments are being made.

A record of the changes observed in the above criteria offered a semiquantitative basis for comparing various therapeutic procedures. It also made possible a direct comparison between the physiologic status of different animals.

## Results

### 1. *The Three Stages of Vascular Reactivity during Shock*

On the basis of the vascular responses observed, our studies[5] have shown that the post-hemorrhagic syndrome consists of three phases.

A. *Hyperreactive, Compensatory Stage:* The immediate adjustment to the reduced blood volume was a widespread constriction of the larger arteries and veins. This was followed by an augmented activity of the terminal muscular vessels, which exhibited an increase in the frequency and amplitude of their vasomotion and an increased responsiveness to the constrictor effect of epinephrine.

B. *Transitional Stage:* In animals bled sufficiently to lower the blood pressure to the 40- to 50-mm. Hg range and allowed to remain in that range for two to three hours, the hyperreactive aspects of the syndrome gradually regressed and eventually were superseded by a state of diminished responsiveness.

C. *Hyporeactive or Decompensatory Stage:* During the several hours of drastic hypotension the responses of the terminal arterioles and precapillaries became impaired and finally depressed. The hyporeactivity in the capillary bed was associated with an inadequate return of blood from the capillary bed to the venous side of the circulation.

### 2. *Refractoriness to Infusion Related to Vascular Dysfunction*

Many investigators have demonstrated that dogs in hemorrhagic shock become with time increasingly refractory to fluid therapy. Our experiments show that the development of this unresponsive condition parallels closely the sequence of the vascular changes observed. It was found that the condition of the capillary bed at the time of fluid administration served as an excellent prognostic guide of the ability of the dog to respond. Thus, during the initial, reversible hyper-reactive stage it was possible to restore the normal dynamics of the capillary circulation by the infusion of any of the following fluids: physiologic saline (3 dogs), 5 per cent bovine albumin (4 dogs), and citrated plasma or whole blood (6 dogs). During the transitional stage, saline infusions became ineffective (3 dogs). During the latter part of the transitional and the early part of the hyporeactive stage bovine albumin also became ineffective (3 dogs). Finally, when hyporeactivity had persisted for at least sixty to ninety minutes, recovery was no longer possible, even with whole blood or plasma, irrespective of whether large amounts (up to 8 or 9 per cent of body weight) were used, or the infusion was prolonged for several hours (18 dogs).

### 3. *Therapy During the Hyporeactive Stage*

A. *Procedure for Evaluating Therapeutic Measures:* Wiggers[6] and Frank and his co-workers[3] have used as their end point the failure of the dog to recover when infused with the blood previously withdrawn. This procedure was found to aggravate the shock condition and made the physiologic state of the animal difficult to evaluate at the time that any supplementary treatment was instituted. The end point used by us was the detection of definitive circulatory criteria in the omentum by microscopic observation. The accuracy of this procedure was tested by subjecting 18 dogs to graded hemorrhage and maintaining them in extreme hypotension until the omental circulation exhibited criteria characterizing hyporeactivity. The dogs were then kept in this state for one to two hours at which time they were infused with citrated whole blood (0.2 per cent sodium citrate) equal to the amount previously withdrawn. Fifteen of the 18 dogs showed a temporary improvement of the peripheral circulation which eventually deteriorated, the dogs collapsing about one to two and one-half hours after the infusion.*

* We have in later studies infused over 50 dogs in the hyporeactive stage as determined by the omental index and found 82 per cent of the animals to be irreversible to whole blood replacement.

B. *Vascular Changes following Replacement of Blood Withdrawn:* The injection during the hyporeactive stage of all of the blood previously withdrawn usually raised the blood pressure to within 10 to 20 mm. Hg of the control level and set up an active flow in the capillary bed. These reactions, however, were transitory and began to wear off shortly after the infusion was stopped. A typical example of this sequence of changes is seen in figure 1, a detailed protocol illustrating this group of dogs. In several instances it was possible by means of repeated infusions at necessary intervals to forestall the slowing of the circulation for as long as three hours. It is of interest to note, however, that although the blood pressure was kept elevated above 80 mm. Hg during this period, there was no return of vasomotion, the arterioles and precapillaries remained refractory to epinephrine, and atony of the terminal arterioles and venules persisted. The continued infusion resulted in an abnormal dilatation of the muscular vessels of the bed, further indicating the loss of their compensatory adjustment reactions. Within forty-five to sixty minutes after the blood had been administered, the capillary flow again became sluggish, considerable backflow from the venules into the capillaries developed, and fatal circulatory collapse ensued within sixty to one hundred twenty minutes thereafter.

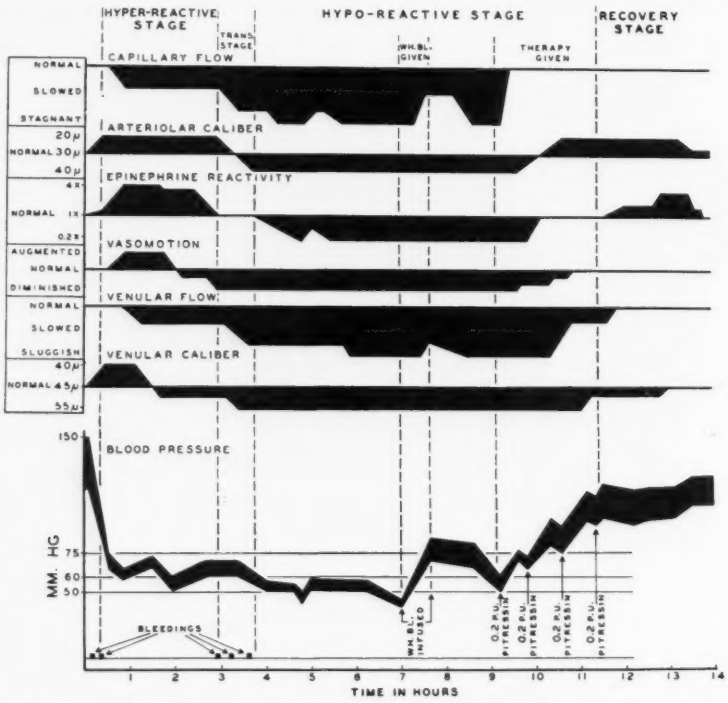


FIG. 1.—TABULATION OF PROTOCOL OF DOG RECEIVING PITRESSIN THERAPY AFTER UNSUCCESSFUL TREATMENT WITH WHOLE BLOOD. Weight, 6 Kg.; anesthesia, 2 mg. morphine sulfate per kilogram of body weight; total blood loss, 41 cc. per kilogram of body weight. Bleeding procedure is indicated in text. The chart shows the changes in six criteria of the omental vessels presented in relation to the blood pressure. The degree of change is expressed by extent of deviation from the normal base-line. Epinephrine reactivity represents the response of the terminal arterioles to the topical application of the drug. Vasomotion, augmented, indicates an increase in both rate and duration of the constrictor phases; diminished vasomotion indicates an increasing predominance of the dilator phase, until the spontaneous caliber changes disappear. Abbreviations are the same as for figure 2.

Only three dogs showed a continued improvement of the omental circulation and ultimately

recovered. It is significant that the improved circulation always preceded the gradual rise of the blood pressure out of shock levels. The sequence of vascular changes leading to the recovery of the omental circulation were as follows:

Irrespective of whether the animals were reversible or irreversible, the omental circulation invariably showed an initial speeding up of flow, which appeared to be of mechanical origin. However, in reversible cases, this was accompanied by the appearance of an improved tone in the small arterioles and precapillaries as evidenced by a narrowing of the vessels and a thickening of the wall. Vasomotion reappeared within twenty to thirty minutes, first in the precapillary branches and later in the metarterioles proper. The reactivity of these vessels to epinephrine returned to normal levels somewhat more slowly, requiring about ninety to one hundred minutes after the start of the infusion. Two to three hours after blood replacement had been completed, the blood pressure was between 95 to 100 mm. Hg and the omental circulation appeared to be normal except for a moderate dilatation of some of the venules and small veins.

C. *Restoration of Blood Volume with Several Blood Substitutes:* Nine dogs were transfused during the hyporeactive stage: 3 with 5 per cent bovine albumin, 3 with an isotonic mixture of albumin and concentrated globulins, and 3 with a solution of 2 per cent sodium succinate. None of the dogs showed a sustained recovery either of the blood pressure or of the vascular reactivity. The omental vessels underwent essentially the same sequence of changes as described following unsuccessful whole-blood therapy. With 5 per cent albumin there was a transient improvement in the capillary circulation, but with no reappearance of vasomotion or restoration of the epinephrine response to normal levels. The addition of varying amounts of a concentrated globulin fraction (dog or beef blood) had no additional beneficial effect. The infusion of 2 per cent sodium succinate was least satisfac-

TABLE 1.—*Effectiveness of Pitressin in Restoring Deranged Circulation in Irreversible Stage of Hemorrhagic Shock*

| Pitressin Therapy | No. of Dogs | Initial Infusion Medium* | Time after Infusion (hrs.) | Condition of Animal B. P. (mm. Hg.) | Omental Circulation | Subsequent Pitressin Infusion (per Kg. body wt.) | Remarks |
|---|---|---|---|---|---|---|---|
| A. None | 18 | Whole blood | 2–3 | 30–45 | Slowed, hyporeactive | None | 2 survived |
| B. After unsuccessful therapy with whole blood | 12 | Whole blood | 1.5–3.0 | 40–50 | Slowed, stagnant | 0.10 p.u. in 2–3 c.c. saline | 8 survived† |
| C. After unsuccessful therapy with agents other than blood | 3 | 5% albumin | 0.5–1.0 | 50–60 | Failing, hyporeactive | 0.20 p.u. in 5 c.c. whole blood | 2 survived |
| | 3 | Globulin + 5% albumin | 0.3–0.7 | 45–50 | Hyporeactive, sluggish | 0.19 p.u. in 5 c.c. whole blood | 3 survived |
| | 3 | 1.8–2.0% succinate sodium | 0.5–0.8 | 45–55 | Hyporeactive, stagnant | 0.20 p.u. in 20 c.c. whole blood | 1 survived |
| D. Combined with whole blood (no previous therapy) | 9 | Whole blood + 0.06 p.u. pitressin/Kg. | 0.5–0.8 | 85–100 | Rapid, normal reactivity | 0.05 p.u. in 2–3 c.c. saline only when necessary‡ | 8 survived |

p.u. = pressor units.

* Sufficient to restore blood volume to normal.

† Blood pressure and peripheral circulation restored to control levels; dogs sacrificed after three to six hours in this condition.

‡ Some dogs required additional injections of pitressin in order to maintain active circulation.

tory, since in 2 of the 3 dogs treated, the peripheral circulation remained almost stagnant throughout. Moreover, the response of the arterioles and precapillaries to epinephrine was actually further depressed by succinate therapy.

D. *Addition of Vasoconstrictor Agents to Infusion:* In view of the demonstrated tendency of the muscular vessels distal to the larger arteries to lose their original compensatory capacity as the state of shock deepened, it was postulated that the addition of a vasoconstrictor or vasotonic agent to the infusion mixture might be of value. A series of pressor drugs were tested, viz., epinephrine, neosynephrin, paredrine, ephedrine, and the S-ethyl derivative of iso-thio-urea. None of these agents proved to be of any sustained therapeutic value for the peripheral circulation.

(a) *Epinephrine.* When injected intravenously into normal control dogs the lowest concentration (0.002 to 0.02 mg. per kilogram of body weight) produced a visible narrowing of the arterioles and precapillaries, whereas the maximum concentration (0.5 to 2.0 mg./Kg.) produced an intense vasoconstriction and almost complete cessation of the capillary circulation. Ten dogs in the hyporeactive stage of shock were given epinephrine in varying dosages and in each of these animals the responses were considerably less than those observed in the controls with comparable dosages. In 4 of these which received intravenously 0.002 to 0.02 mg. of epinephrine per kilogram of body weight, there was no significant improvement either in the blood pressure or in the omental circulation. In 5 of the dogs, given higher dosages of epinephrine (.04 mg. to 2.0 mg./Kg.), there occurred a transient vasoconstriction of the larger arterioles, accompanied by a rise in the blood pressure from a level of 35 to 45 mm. Hg to 60 to 70 mm. Hg. This was followed by a speeding up of blood flow for a period of five to ten minutes. In one dog the same dose of epinephrine (0.002 mg./Kg.) was administered during the hyperreactive, the transitional, and twice during the hyporeactive stage. The vasoconstrictor effects of the third and fourth injections were significantly less than those elicited by the first two injections.

(b) *Neosynephrine and Ephedrine.* Injections of 0.1 to 6.0 mg. of *neosynephrin* per kilogram of body weight were given to 12 dogs in various stages of shock. In the normal dog these amounts produced a transient pressor effect of 10 to 100 mm. Hg respectively. In 2 dogs in the hyporeactive stage of shock concentrations below 0.3 mg. per kilogram of body weight were without effect. In 8 other dogs in shock, higher concentrations of the drug produced only a transitory speeding up of circulation through the capillary bed with no significant alteration in the tone or reactivity of the vessels.

Neosynephrin was more effective than epinephrine when given after infusion. In 2 dogs, which had been transfused with blood and were again showing signs of deteriorating, injections of 0.5 to 10.0 mg. of neosynephrin per kilogram of body weight stopped the fall in blood pressure and maintained it at a level compatible with good blood flow for twenty to thirty minutes. The animals eventually became refractory to repeated doses of the drug.

*Ephedrine* in concentrations of 0.1 to 0.5 mg./Kg. had no sustained restorative action on the omental circulation of 3 dogs in the hyporeactive state of shock.

(c) *Paredrine.* Paredrine (20.0 to 30.0 mg./Kg. i.v.) produces a pressor effect in control dogs with only a moderate vasoconstriction of the small arteries and veins visible in the omentum. Eight dogs in shock received from 10.0 to 50.0 mg. of paredrine. Six of the animals received the drug before infusion and showed only a transitory increase in pressure and circulation. Two animals were given 10.0 mg. after the blood pressure had risen to 75 to 80 mm. Hg following a blood transfusion. The drug raised the blood pressure to 100 to 110 mm. Hg and considerably speeded the circulation through the capillary bed. This effect persisted for about twenty minutes and then wore off. As with other pressor agents, repeated injections in the hyporeactive stage of shock were progressively less effective.

(d) *S-ethyl-iso-thio-urea.* Three dogs received injections of 7.0 to 200.0 mg. of this drug during the hyporeactive stage of shock, with no

sustained improvement of either the omental circulation or the blood pressure.

F. *Addition of Vasotonic Agents:* From the above experiments it was obvious that all the pressor drugs which were used, produced their maximal pressor effect at the expense of the peripheral circulation. Peripheral blood flow was curtailed as a result of excessive vasoconstriction. Experiments were therefore carried out with what may be termed "vasotonic therapy," in which the primary consideration was the use of drugs in dilutions sufficiently low to produce a barely perceptible narrowing of only the terminal blood vessels. Such concentrations had no constrictor effect on the larger blood vessels. Of several agents tested the most promising were found to be pitressin and angiotonin. Only six experiments were carried out with angiotonin owing to the difficulty of obtaining large amounts of this renal pressor agent. A total of forty-eight experiments were carried out with pitressin administered by several different procedures.

(a) *Angiotonin.** The intravenous injection of 4 cat units of angiotonin (0.2 cc. in 5.0 cc. of saline) into 2 dogs during the hyporeactive stage of shock produced a transient increase in capillary circulation within two to four minutes and a definite narrowing of the arteriolar vessels. The blood pressure then gradually rose from 30 to 45 mm. Hg to 45 to 50 mm. Hg for about twenty minutes. This was less than the response obtained in normal dogs prior to bleeding. It was then decided to attempt to maintain a constant level of angiotonin in the blood by a slow intravenous infusion. In three dogs, up to 120 cat units of angiotonin were administered by a continuous drip infusion in 60 to 100 cc. of saline over periods of thirty to sixty minutes. Throughout the infusion the peripheral circulation improved considerably and in one dog vasomotion was temporarily reestablished. However, fifteen to twenty minutes after the infusion was ended, the circulation had again deteriorated to shock levels. One dog which had been transfused during the hyporeactive stage with all of the blood previously withdrawn and had again showed signs of circulatory failure, was given 20 cat units of angiotonin by repeated injections with no sustained beneficial effect.

(b) *Pitressin in Subpressor Concentrations.* Pitressin, in a pressor concentration of more than 0.15 p.u./Kg. body weight, was definitely contraindicated because it not only exaggerated the constricted state of the larger blood vessels but also exerted a deleterious effect on the heart. On the other hand, pitressin in concentrations which have no constrictor effect on the larger blood vessels and which are just below that exerting a constrictor effect on the arterioles, that is, *in subpressor concentrations*, produced a striking improvement in the peripheral blood flow. In a series of experiments based on reactions of the omental vessels in the dog, the concentration of pitressin best suited for such an improvement was found to be about 0.05 to 0.1 pressor units, per kilogram of body weight. The most satisfactory results were obtained with a mixture of pitressin and whole blood administered by a slow intravenous infusion.

In the experiments, pitressin was given by the following procedures:

1. Pitressin added to initial fluid infusion. Nine dogs were subjected to graded hemorrhage until they were judged to be irreversible by the hyporeactive condition of their omental circulation. The dogs were then infused with an intravenous drip of blood containing 0.05 p.u. pitressin per kilogram of body weight over a period lasting about sixty to ninety minutes, until the original volume had been restored. The typical response to such an infusion is shown in a protocol (fig. 2) of one of the dogs of this series. The blood pressure rose to about 100 to 110 mm. Hg and persisted at that level after the infusion had been completed. The blood flow in the omentum began to improve within five to ten minutes after starting the infusion. This is considerably earlier than occurs when blood alone is being infused during the irreversible stage. More significant than the early recovery of the blood flow were the gradual reappearance of vasomotion of the terminal arterioles and precapillary sphincters, a return to normal levels of their epinephrine

* Prepared by The Lilly Research Laboratories, Eli Lilly and Company.

reactivity, and a recovery of the relaxed arterioles to a partially constricted state.

In 5 of the subjects, about one hour after the infusion, the flow began to slow down, especially on the venous side. The blood pressure fell to about 80 to 85 mm. Hg. A second injection of pitressin, 0.2 p.u. in 5.0 cc. saline was then administered. This improved the peripheral blood flow and the blood pressure grad-

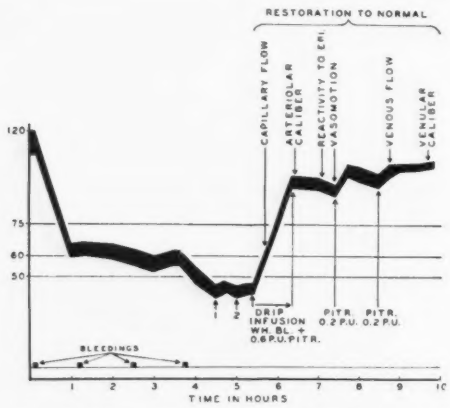


FIG. 2.—WHOLE BLOOD PITRESSIN THERAPY. Protocol of dog subjected to graded hemorrhage and given pitressin therapy during the "irreversible" stage. Weight, 9 Kg.; anesthesia, 30 mg. pentobarbital per kilogram of body weight; total blood loss, 32 cc. per kilogram of body weight. During the fifth hour, two test infusions of 25 cc. each were given at points 1 and 2. Both blood pressure and circulation failed to respond indicating pronounced hyporeactivity. During the sixth hour, the previously withdrawn blood was returned by a drip infusion containing 0.6 pressor units (p.u.) of pitressin. Above the blood pressure graph are recorded the recovery in sequence of the several vascular reactions in the omentum. P.U. = pressor units, pitr. = pitressin, and wh. bl. = whole blood.

ually returned again to the 90 to 100 mm. Hg level. In 3 of these dogs it was found necessary to give a third and, in one, a fourth injection of pitressin. In none of the dogs did the total amount administered exceed 0.15 p.u. per kilogram of body weight, a quantity which was still subpressor.

A summary of these experiments together with the remaining pitressin data is given in table 1. This table shows that out of the total of 9 dogs the circulation of 8 could be restored to control levels. The elevated blood pressure and peripheral blood flow persisted at comparatively normal levels for about four to six hours, at which time the dogs were sacrificed.

2. Pitressin subsequent to whole blood infusion. These experiments were performed on 12 dogs to determine whether pitressin would be effective if administered after the dogs had not responded to whole blood infusion. Figure 1 is a protocol of one of these dogs and illustrates the vascular changes in the omentum and the effect produced by the subsequent pitressin therapy. The infusion of blood occasioned a rise of the blood pressure and a partial recovery of the flow in the capillary bed without a comparable reinstatement of its functional activity (return of vasomotion and of normal epinephrine reactivity). About two hours after the infusion had been given, the blood pressure had fallen to 75 mm. Hg and continued to fall while the omental circulation became increasingly hyporeactive.

At this time, pitressin (0.1 p.u. in 10 to 20 cc. saline) was injected intravenously. This was rapidly followed by a speeding up of the capillary flow and by a progressive recovery of arteriolar activity, viz., a partial narrowing of the vessels characteristic of their normal tonic state. In several cases (table 2) a second and a third injection of pitressin (each 0.2 p.u. in 2.0 cc. saline) were given at intervals of about forty minutes. Eight of the dogs showed a considerable improvement in omental reactivity which was maintained for four to six hours. The dogs were then sacrificed at which time their blood pressure was from 90 to 110 mm. Hg. Four of the dogs showed only a partial recovery of their vascular reactions and succumbed about one to three hours later.

3. Pitressin subsequent to unsuccessful therapy with agents other than blood. In the course of our therapeutic experiments a number of dogs, in the hyporeactive stage, were infused with several different blood substitutes: 5.0 per cent albumin, an isotonic mixture of varying proportions of albumin and globulin, and a solution of 2.0 per cent sodium succinate. All the dogs remained in the hyporeactive state, whereupon they were given pitressin. The results are recorded in table 2. Of the 9 dogs

treated in this way, 6 showed recovery of their circulatory reactions until they were sacrificed about four to five hours after the initiation of therapy. The circulatory changes were essentially the same as those observed in the other groups of animals.

vessels.[7] In these studies no direct causal relationship was established between the vascular phenomena observed through the microscope and the course of the shock syndrome. However, the remarkable uniformity with which the two sets of events occur through-

TABLE 2.—*Therapy during Irreversible Stage of Hemorrhagic Shock*

| Dog | Anesthesia (mg./Kg.) | Blood Loss (cc./Kg.) | B. P. during Shock (mm. Hg.) | | Circulation in Omentum | Therapy | | Time after Initial Therapy (hrs.) | Effects of Therapy | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 50-75 (hrs.) | 45 (hrs.) | | Fluid Infusion (cc./Kg.) | Pitressin (p.u./Kg.) | | B.P. (mm. Hg) | Circulation in Omentum | Remarks |
| A. *Whole Blood* | | | | | | | | | | | |
| *64 | Morphine, 12 | 37 | 3.5 | 1.5 | Hyporeactive, sluggish | Whole blood, 35 | None | 1.2 | 60–75 | Sluggish, stagnant | Hyporeactivity persists; died 1.5 hrs. later |
| B. *Pitressin after Unsuccessful Therapy with Whole Blood* | | | | | | | | | | | |
| *68 | Morphine, 12 | 39 | 3.6 | 2.0 | Hyporeactive, stagnant | *Initial* Whole blood, 38 | — | 2.0 | 60–70 | Sluggish, hyporeactive | Marked stagnation in venules |
| | | | | | | *Subseq.* Saline, 8 | 0.19 | 3.8 | 96–100 | Good blood flow | Capillary bed normal, sacrificed 0.5 hr. later |
| C. *Pitressin after Unsuccessful Therapy with Agents other than Blood* | | | | | | | | | | | |
| *29 | Morphine, 12 | 36 | 4.5 | 1.5 | Hyporeactive stagnant | *Initial* 5% albumin, 36 | — | 0.8 | 50–64 | Failing hyporeactive | Arterioles dilated |
| | | | | | | *Subseq.* Whole blood, 8 | 0.20 | 3.5 | 80–100 | Markedly improved | Sacrificed 0.5 hr. later |
| *51 | Pentobarb. 30 | 3.0 | 3.0 | 1.1 | Hyporeactive sluggish | *Initial* Globulin-albumin, 35 | — | 1.0 | 44–50 | Poor, failing | Responsiveness subnormal |
| | | | | | | *Subseq.* Saline, 10 | 0.04 | 2.5 | 64–75 | Slowed | Venular flow still poor |
| | | | | | | Whole blood, 6 | 0.08 | 4.8 | 100–115 | Good | Reactivity normal, sacrificed 1.0 hr. later |
| *50 | Pentobarb. 25 | 31 | 3.0 | 1.3 | Hyporeactive, stagnant | *Initial* 1.8 Na succinate | — | 1.0 | 56–65 | Very poor, stagnant | Almost no flow in vessels |
| | | | | | | *Subseq.* Whole blood, 18 | 0.15 | 4.0 | 100–120 | Normal, rapid | Arterioles narrow; sacrificed 0.5 hr. later |
| D. *Pitressin-Whole Blood (no previous therapy)* | | | | | | | | | | | |
| *92 | Morphine, 12 | 39 | 4.0 | 2.5 | Hyporeactive, sluggish | Whole blood, 39 | 0.10 | 4.1 | 110–125 | Restored, excellent | Sacrificed 24 hrs. later |

## DISCUSSION

The establishment of clearly defined functional changes in the minute blood vessels of the omentum during shock made possible a new approach to the development of therapy for this syndrome. Our previous investigations on hemorrhagic and tourniquet shock called attention to the nature of the breakdown of the functional activity of the visceral blood

out the progression of shock, makes it probable that the observed vascular dysfunction is a critical defect contributing to the circulatory insufficiency. In other studies from this laboratory,[8] evidence of another character has been obtained which indicates a causal relationship between these vascular episodes and the metabolism of specific hepatorenal factors.

With regard to the causal relationship of the

disturbance in the peripheral blood vessels and the blood pressure after therapy, the following observations are pertinent. It was possible temporarily to raise the blood pressure by the infusion of large amounts of fluid or by the injection of vasodepressor drugs without influencing the unfavorable outcome of the shock. In these dogs an accelerated blood flow developed only subsequent to the increased blood pressure. In those animals in which therapy was successful, an improvement in peripheral blood flow of considerable magnitude occurred at a time when changes in blood pressure were still minimal. Later, as an adequate peripheral blood flow was re-established, the blood pressure began to show a steady rise. Conversely, with the progression of shock, a deterioration of the peripheral circulation usually *preceded* the subsequent drop in the blood pressure and the circulatory collapse during the latter stages of the syndrome.

The necessity for overcoming the decompensatory vascular changes, which develop during the "irreversible" stage, is clearly indicated by the close correlation between the course of the syndrome following therapeutic measures and the degree of functional repair in the peripheral vascular system. In all animals in which the response to therapy was unfavorable and peripheral circulatory collapse ensued, no improvement in the omental circulation occurred, except for a transitory speeding of flow. This is in striking contrast to the course following favorable therapy during which a progressive restoration of the functional responses of the vessels accompanied the gradual improvement in blood flow and resulted in a return to normal of the integrated activity of the capillary bed.

The use of the exteriorized omentum for microscopic study placed several limitations on the experimental procedure. The subsequent effects of therapy could be followed only for four to six hours. Therafter, prolonged exposure of the omentum added the possibility of nonspecific vascular deterioration. Furthermore, the animals, when brought out of shock, became restless and required repeated anesthesia, a procedure which complicated the post-therapeutic course. The experiments were therefore terminated at this time without testing the long-term value of any of the therapeutic procedures. Although the therapeutic implications of such experiments are limited, the studies clearly indicate that successful therapy must restore the circulatory efficiency of the peripheral vascular system. Anesthetized dogs, transfused with blood alone during the irreversible stage of hemorrhagic shock, invariably again went into fatal circulatory collapse within four to six hours. In contrast, animals treated with pitressin in vasotonic but subpressor concentrations showed at the end of four to six hours a markedly improved peripheral circulation with a restoration of many of the features of normal functional activity. These experiments would, therefore, seem to bear directly on the ultimate direction towards which treatment of "irreversibility" should be directed.

The administration of fluid sufficient to replace the deficient blood volume was of value early in shock before the mechanisms for peripheral vascular adjustment had deteriorated. Such nonspecific measures became less effective as the shock deepened. The fact that blood plasma was effective for a longer period than saline, albumin, or gelatin indicates that plasma exerts a physiologic effect beyond that imparted by its bulk and colloidal osmotic properties. Over the short range of our experiments, no immediate superiority could be detected between plasma as opposed to whole blood. There is, however, ample evidence in the literature that the anemia which frequently follows hemorrhagic shock is greatly benefited by whole blood therapy.[9]

Mechanical restoration of the peripheral circulation is not sufficient, by itself, to correct the metabolic disturbances which during shock are inflicted by prolonged periods of inadequate circulation on organs such as the liver, kidney, heart, and brain. Recent work by Shorr, Zweifach, and Furchgott[10] has demonstrated that the vascular decompensation in the omentum is not solely the result of local impairment of blood flow but in large part can be referred to blood-borne vasodepressor principles (VDM) which originate in the liver and skeletal muscle. The therapeutic problem is therefore twofold. First, the correction of vascular dysfunction

resulting from the local accumulation of nonspecific metabolites and from specific vasodepressors (VDM) arising in organs such as liver and skeletal muscle; second, the correction of the metabolic defects in these organs as a result of which VDM continues to be elaborated and maintained at high levels in the blood.

None of the pressor agents employed (epinephrine, neosynephrin, ephedrine, or paredrine) were of value in counteracting the atony of the peripheral vessels. The progressive decrease in the responsiveness of hypotensive animals to pressor agents has been discussed by Frank and co-workers.[11] Our data indicated that the impaired responsiveness is referable, at least in part, to the hyporeactive state of the muscular components of the capillary bed. Whatever pressor action these agents displayed during the terminal stages of shock, was the result of vasoconstriction of the larger blood vessels, the direct effect of which was a further curtailment of the circulation in the tissues proper. Additional evidence for the contraindication of pressor drug therapy during the hyporeactive stage was the stasis which developed in the larger veins during the period of elevated blood pressure induced by these drugs. It is of interest to note that, following transfusion, the refractoriness to pressor agents wore off in those cases which were reversible, whereas the pressor response remained depressed in animals which proved to be irreversible and eventually died.

Angiotonin gave some evidence of being a promising therapeutic agent. Because of the relatively few experiments done, we have insufficient data for this renal pressor substance. Page[12] has reported that dogs subjected to hemorrhage were refractory to small doses of angiotonin (0.2 cc., or approximately 6 cat units). In our experiments, although the vascular response to angiotonin became less pronounced during the hyporeactive stage of shock, the administration of larger amounts (up to 120 cat units) by slow intravenous infusion produced a striking improvement of blood flow, despite the fact that the blood pressure rose only 30 to 40 mm. Hg above shock levels. Unfortunately, the effects were only temporary and wore off each time that the infusion was stepped.

Pitressin added in subpressor concentrations to the blood infusion brought about a significant extension of the period of effectiveness of whole blood therapy. The indications from the omental vascular criteria are that pitressin, administered subsequent to unsuccessful whole blood infusion, is not as effective as when the pitressin is administered together with the whole blood. Although these small amounts have no obvious direct pressor action, they are within the range (.02 p.u./Kg.) which produces a profound effect in unbled dogs.[13] Frank, Seligman, and Fine[3] were unable to obtain significant therapeutic results with pitressin when administered to dogs already found to be irreversible to whole blood or to the administration of succinate or of bicarbonate therapy. They found no increase in the number of animals which could be recovered by pitressin used subsequent to these experiments. The question remains whether the method used by them (that of testing pitressin only after the dog had failed to respond to whole blood) is appropriate for an evaluation of shock therapy. This drastic procedure involved subjecting the dog to deep shock twice in succession, first after the bleeding procedure and, second, after the temporary effects of the unsuccessful transfusion. When such procedures were used in our studies, considerable stasis was observed in the collecting venules and capillaries following the failure of the transfusion. As a result, large areas of the capillary bed remained in stasis and inactive throughout the subsequent period of therapy.

Our results with pitressin indicate the desirability of effecting a sustained improvement in the peripheral circulation through a vasotonic action on the terminal arterioles and precapillaries. Although pitressin has other pharmacologic effects which may militate against it being the agent of choice in irreversible shock therapy, it unquestionably prolonged the survival, for at least three to four hours, of dogs which otherwise would have died. What appears to be most significant about these experiments is the demonstration that functional repair of the peripheral vascular bed is

a necessary prerequisite for recovery from shock. It was our hope that through the use of vasotonic agents such as pitressin, we could maintain the adequate circulation for sufficiently long periods to allow the animal to repair these metabolic lesions. Our observations, being confined to a three- to six-hour period after the institution of pitressin, did not permit any long-term evaluation of this thesis. It is possible that the inadequacy of pitressin therapy in certain of our shocked animals may be ascribed to the continued elaboration of VDM. This would indicate that the metabolic derangements in the tissues are not reversed by the comparatively short periods of improved circulation in these experiments. Frank and co-workers[14] by in vivo perfusion experiments obtained evidence that perfusion of the liver of shocked dogs with arterial blood from a normal donor dog for three to four hours (range from three to eight hours) is often sufficient to counteract the development of irreversibility. The recent isolation of VDM and its identification as ferritin by Mazur and Shorr[15] opens up the possibility of developing measures for counteracting this specific principle and isolating the enzyme systems responsible for its inactivation.

## Conclusion

Our experiments call attention to the prime necessity of restoring the normal functional behavior of the capillary circulation of animals in hemorrhagic shock and indicate the value in such conditions of vasotonic agents such as pitressin which appear to accelerate the recovery of the vascular bed.


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# Studies of the Renal Circulation

*By* Joseph R. Kahn, M.D., Leonard T. Skeggs, Ph.D., and Norman P. Shumway, M.D.

This work represents an attempt to confirm reported observations of a juxtamedullary by-pass in the kidneys of animals subjected to various physiologic procedures and to shock. Rabbits injected with epinephrine, pitressin, renin and hypertensin, made hypotensive by bleeding and inhalation of amyl nitrite, and after stimulation of one sciatic nerve, were injected with india ink. The kidneys were removed and studied for the paths of blood flow. No evidence of a by-pass mechanism through the juxtamedullary glomeruli was found.

TRUETA and his co-workers[1] have presented a new concept of the renal circulation. They believe that in certain physiologic and pathologic conditions the circulation of the blood through the renal cortex can be either diminished or totally arrested, while the circulation through the juxtamedullary glomeruli and medulla continues. The diversion of the blood from the cortex to the medulla is said to occur when there exist one or more of the following conditions: (1) constriction of the peripheral portions of the interlobular arteries; (2) dilatation of the vessels associated with the juxtamedullary glomeruli; (3) degeneration of the juxtamedullary glomeruli with the formation of arteriae rectae verae which are similar to "Ludwig's arteries" in the remainder of the cortex; (4) obstruction of the glomeruli in the peripheral zones of the renal cortex.

The medullary circulation they term "the lesser circulation" or "medullary by-pass," which consists of: (1) the most proximal portions of the interlobular arteries; (2) the first branches of the interlobular arteries, which are the afferent arterioles of the deep, or juxtamedullary, glomeruli; (3) the juxtamedullary glomeruli; (4) the efferent arterioles of the juxtamedullary glomeruli, which lie partly in the corticomedullary zone and partly in the subcortical zone of the medulla; (5) the arteriae rectae, and, probably to a lesser extent, the intertubular capillary network, which form part of the vasa recta system; (6) the venous components of the vasa recta which empty into (7) the proximal ends of the interlobular veins and the arcuate veins.

Trueta and collaborators state that in animals, under certain experimental conditions, they have demonstrated the existence of a "medullary by-pass" which is similar to physiologic and pathologic states occurring in man. They studied the course that the blood took in its passage through the kidneys by means of the injection of radio-opaque materials, various suspensions of dyes, ink, and colloidal substances. These were injected into the arterial and venous systems of the animals. Arteriograms of the kidneys were taken during life, radiographs of excised kidneys were made, and a method of taking microradiograms was devised.

During their experimental procedures many of the kidneys were exposed and their superficial surfaces and renal veins observed to determine the presence of the injected material. Blanching or paling of the surfaces of the kidneys occurred in the animals in many of their experiments, and, as a frequent accompaniment of this phenomenon, a pulsating arterial stream of blood was found in the renal vein, as was also a stream of the injected material. The blanching of the renal cortex, together with the observation of a pulsating arterial stream of blood in the renal veins, was interpreted by Trueta and his associates as a "by-pass" of the renal cortex by the blood and injected material. The renal pedicles were ligated; the kidneys were removed from the animals, sectioned, and examined to determine the route that the blood or injected mass traversed in its

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passage through the kidneys. Frozen sections of the kidneys of varying thickness, both stained and unstained, as well as paraffin sections of the usual thicknesses were prepared. These sections were examined by means of the binocular dissecting microscope and single-objective microscope to determine the location of the blood or injected material in the kidneys. According to Trueta and his co-workers, the blood and injected materials were found occupying the vascular channels composing "the lesser circulation" of the kidneys when there existed, prior to the death of the animal, blanching of the renal cortex and a pulsating arterial stream of blood in the renal veins.

Trueta and his associates state that in the following experiments the circulation through the cortex of the kidneys was either diminished or totally arrested, while the circulation through the juxtamedullary glomeruli and medulla continued: (1) stimulation of the central end of the divided sciatic nerve; (2) after severe rapid hemorrhage; (3) after injections of adrenalin, pituitrin, and pitressin; (4) during inhalation of amyl nitrite.

They attributed the diversion of blood from the cortex to the medulla, in the first three series of experiments, to constriction of the peripheral portions of the interlobular arteries, while in the fourth experiment the diversion of blood was due to dilatation of the vessels associated with the juxtamedullary glomeruli. By these and similar experiments Trueta and his co-workers believe they have shown that large numbers of glomeruli can be excluded from the circulating blood. The phenomenon of glomerular intermittence in the mammalian kidney may be on a vastly greater scale, according to these investigators, than in the amphibian, as reported by Richards. It is clear that the change in the course of the renal circulation outlined by Trueta and associates could be of great importance in the interpretation of normal renal physiology as well as of pathologic states due to diseases of the kidney, or of changes in other portions of the body, with secondary effects on the renal vascular pattern.

Because of the importance of the conclusions drawn by these authors, and our own interest in hypertension and renal circulation, we repeated some of their experiments. In addition, we used injections of renin and hypertensin, for the production of brief experimental rises in blood pressure, to determine whether these substances produce any changes in the pattern of blood flow through the kidneys during the periods in which the blood pressure is elevated. Thus, some of the physiologic conditions which are said to determine the by-pass of renal cortex were put to the test by means of these anatomic studies.

## Experiments

*Method.*—Rabbits were used in all of our experiments during which they were anesthetized with intravenous Nembutal and given 1,000 units of heparin. One of the carotid arteries was cannulated and the blood pressure recorded on a moving drum. The contrast medium used for studying the vascular pattern of the kidneys was Higgins india ink, recommended by Trueta and colleagues. Fifty to 80 ml. of ink were injected under pressures averaging about 10 mm. Hg higher than the arterial pressure at the time of the injection into the distal portion of the abdominal aorta (below the renal arteries) through a cannula pointing towards the heart. The renal pedicles were ligated immediately after the injection was completed. The kidneys were then removed and placed in 10 per cent formalin. After two hours in formalin, the kidneys were sectioned and fixation was allowed to continue for twenty-four to forty-eight hours longer. Numerous specimens were taken from all portions of the kidneys. Blocks were embedded in paraffin, sectioned, and stained in the usual manner. Frozen sections of larger blocks of the kidneys were made and examined. We found that in our hands frozen sections of 100 to 200 micra were the most satisfactory. These sections were then run through the alcohols, cleared in xylol, and mounted in Clearite. Slides prepared in this manner could be examined either with the dissecting binocular microscope or the single-objective microscope with direct or transmitted light.

*Experiment 1. Normal Controls.*—Twelve control animals were used. Ink was injected into the distal end of the abdominal aorta. The renal pedicles were ligated immediately and the kidneys removed.

*Result:* In the 12 control animals all the glomeruli and the other structures of the cortex were well filled, but not intensely, with ink, while in the medulla only a few of the vasa recta contained ink (fig. 1).

*Experiment 2. The Effect of Epinephrine.*—Twelve animals were injected with epinephrine, 0.15 mg. per kilogram of body weight. Members of one group received only one injection, and, at the height of the rise of blood pressure, ink was injected and the animals were sacrificed. The animals of the other group received either repeated injections or a continuous intravenous infusion of epinephrine. India ink was injected, and some of the animals were sacrificed during the following stages: (1) while the blood pressure was rising, (2) while the blood pressure was being maintained at a moderately high level, and (3) during the period in which the blood pressure was falling.

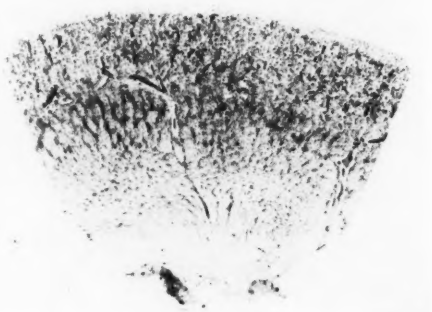

FIG. 1.—The usual appearance of the renal circulation of a normal anesthetized rabbit injected during life with india ink (×4).

*Result:* In the majority of the animals which received epinephrine, circulation through the kidneys apparently ceased during the period in which the blood pressure was elevated. At the height of elevation of blood pressure, ink was present in the larger branches of the main renal arteries, but none was found either in the cortex or the medulla. In the animals in which some blood continued to circulate through the kidneys, or the circulation had been re-established, the ink was found to be distributed in the same fashion as in the normal control series. Thus, there was no indication of a "medullary by-pass" at any stage after the injection, nor was there any evidence that a larger proportion of blood was passing through the medulla than in the normal animals.

*Experiment 3. The Effect of Pitressin.*—Twelve animals were given injections of pitressin, 0.75 to 2 units per kilogram of body weight. They were injected with ink and sacrificed during the following periods: (1) while the blood pressure was still rising, (2) at the height of the rise of the blood pressure, and (3) during the period in which the pressure was falling.

*Result:* The animals which had received injections of pitressin differed from the controls and the other experimental groups of animals (except those that received injections of renin or hypertensin) in that the cortex, medulla, and juxtamedullary glomeruli and their efferent arterioles were well filled with ink. The vasa recta in the medulla were distinct and their arterial, venous, and capillary components were also well filled with ink (fig. 2).

*Experiment 4. The Effect of Amyl Nitrite Under Ordinary Conditions.*—Ten animals were given amyl nitrite by inhalation, and the kidneys injected with ink at the following stages: (1) while the blood pressure was falling, (2) at the time that the blood pressure had reached its maximum drop, and (3) when the blood pressure began to rise, after the administration of the drug had been stopped.

*Result:* The kidneys from the group of animals which received inhalations of amyl nitrite differed from the kidneys of the other animals in two respects: (1) The entire vascular bed of the cortex, including the glomeruli, was greatly dilated and filled with a large amount of ink. (2) The large and abundant venous channels in the subcortical zone of the medulla were also strikingly filled with ink. The entire cortex and the subcortical medullary zone contained more injected material than did the corresponding areas in any of the other groups. The vasa recta were empty (fig. 3).

*Experiment 5. The Effect of Amyl Nitrite Under Special Conditions.*—To eliminate any change in the vascular pattern of the kidneys due to a rise in venous pressure, 4 more rabbits were given amyl nitrite by inhalation. When the blood pressure had dropped significantly, following the administration of the drug, the renal vein of one kidney (the left) was clamped near the vena cava and cut between the kidney and the clamp while the right renal vein was tied off immediately after the injection of the ink. The injection of the india ink was begun simultaneously with the section of the renal vein. Although the renal vein was cut across, there was but little bleeding from it, and but little ink came through in this blood.

*Result:* Although the venous pressure rose in the vena cava during the inhalation of the drug, there was no rise in venous pressure in the left kidney because of section of the renal vein. No indication of a "medullary by-pass" was demonstrated in either kidney of any of these 4 animals. In the sections taken from the left kidneys, there were ink-free areas in the cortex, and areas in which the glomeruli and intertubular capillary network were moderately well filled. It was found that the uninjected areas of the cortex were supplied by the interlobular arteries arising from the distal portions of the "arcuate arteries," while the ink-filled cortical areas were

supplied by the interlobular arteries arising from the proximal portions of these vessels (fig. 4).

*Experiment 6. The Effect of Low Blood Pressure Due to Bleeding.*—Ten animals were bled from the carotid artery. The blood was allowed to flow from a T tube inserted into the tubing which connected the cannula in the carotid artery with the mercury manometer. The amount of blood removed from the animals varied from 50 to 75 cc. The animals were injected with ink when their blood pressures had dropped significantly.

*Result:* In all 10 animals the ink was normally distributed throughout the cortex and medulla, but there was a marked decrease in the amount of injected ink. There was no indication of a medullary by-pass (fig. 5).

*Experiment 7. The Effect of Stimulation of the Central End of the Severed Sciatic Nerve.*—In 11 animals the central end of the severed sciatic nerve was stimulated by faradization for periods varying from one and one-half to five minutes, during which time they were injected with ink and sacrificed.

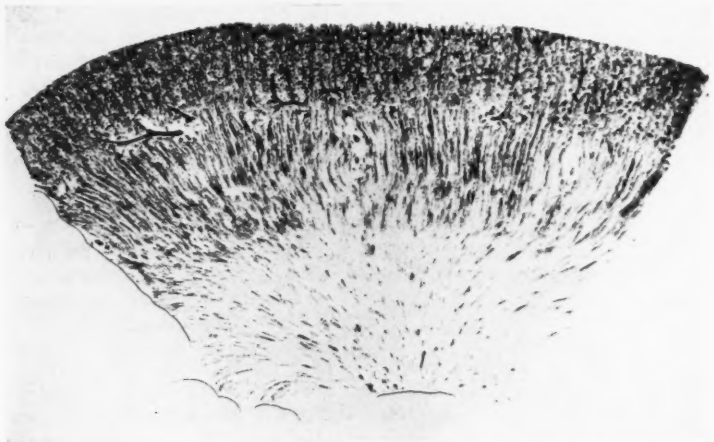

FIG. 2.—Appearance of the cortex and medulla in a rabbit injected with ink at the time of maximum rise of blood pressure following an injection of pitressin (X5).

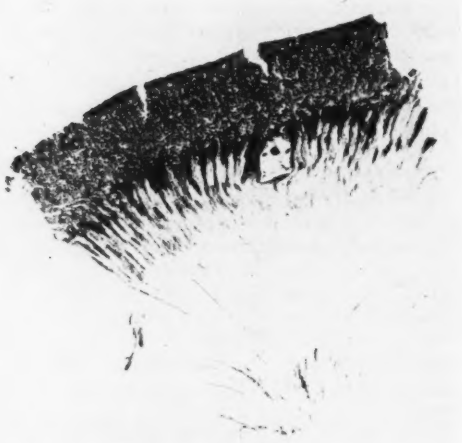

FIG. 3.—Appearance of cortex and medulla at the time of the greatest fall of blood pressure following the inhalation of amyl nitrite and injection of ink (×4).

*Result:* Eight of the 11 rabbits, in which the central ends of the cut sciatic nerves were stimulated by faradic current, had a normal distribution of ink in the cortex and medulla of the kidneys.

In the 3 remaining animals the peripheral portions of the renal cortex were not filled with ink. Many of the glomeruli in the deep zone of the cortex, and many of the juxtamedullary glomeruli were well filled, as were their efferent arterioles and the capillary beds of their corresponding medullary rays. The ink in the medulla was present in radially arranged vessels constituting the arteriae rectae of the corresponding ink-filled juxtamedullary glomeruli, the venae rectae, and, to a lesser extent, the intertubular capillary network comprising the remaining vascular bed of the vasa recta system. Ink-free areas in the deep zone of the cortex alternated with ink-filled areas. In many places the medulla beneath the unfilled cortex was also free of ink. In these 3 animals there was marked vasoconstriction of the main renal arteries and their branches, including their arcuate portions, with a consequent reduction in the size of the renal vascular bed (fig. 6).

The marked contraction of these vessels was best seen in paraffin sections stained with hematoxylin and eosin, or with a combination of Weigert's and van Gieson's stain. In such sections the lumen is

greatly constricted, the internal elastic membrane is wrinkled, and the media is thickened, due to the contraction of the smooth muscle. The lumen of the interlobular arteries, on the other hand, is dilated, their walls are thin, the internal elastic lamina is not and the animals were sacrificed during the following periods: (1) while the blood pressure was still rising, (2) at the height of the rise of the blood pressure, and (3) during the period in which the pressure was falling.

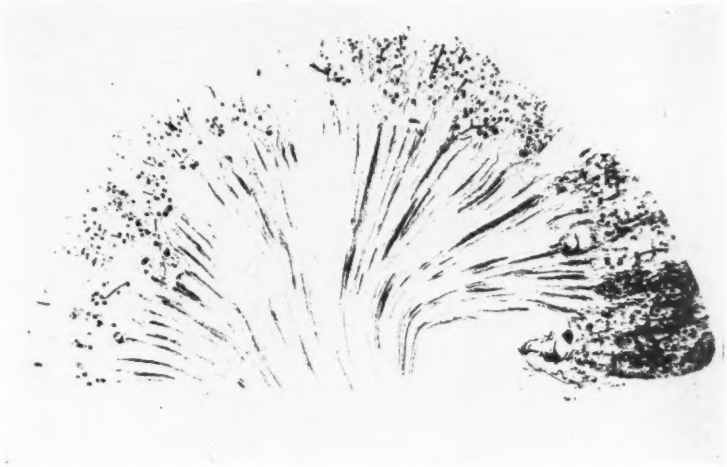

FIG. 4.—The patchy appearance of the cortex and medulla during the inhalation of amyl nitrite following simultaneous injection of ink and section of the renal vein (×7).

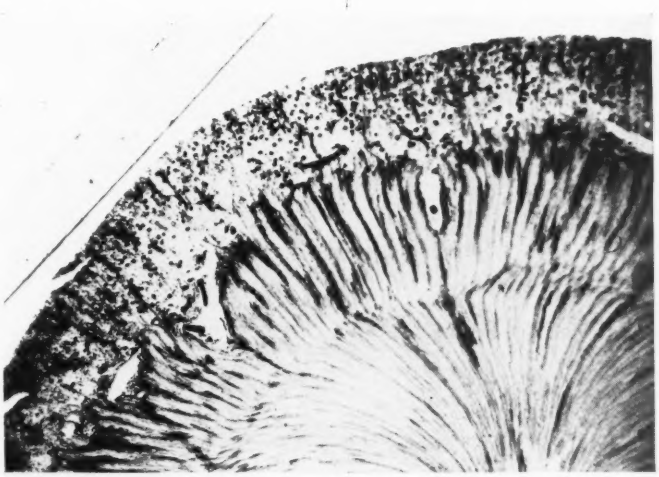

FIG. 5.—Appearance of the cortex and medulla in a rabbit injected with ink at the time of the maximum fall in the blood pressure due to acute hemorrhage (×12).

wrinkled, and the smooth muscle of the media is not contracted.

*Experiment 8. Effect of Renin.*—Twelve rabbits received varying amounts of renin by intravenous injection. Renin and hypertensin were prepared by the method of Katz and Goldblatt.[2] Ink was injected

*Result:* No "medullary by-pass" was recognized in any animal. All of the cortical glomeruli were well filled, as was the cortical intertubular capillary network. The juxtamedullary glomeruli were prominent, as were also their large efferent arterioles. All of the components forming the vasa recta system in the

medulla were well filled. The vessels in the outer zone of the medulla (Peters[3]) contained more injected material than did the corresponding areas in any of the animals subjected to the other experiments. When the blood pressure was elevated as a result of the administration of renin, the injected material passing into the arterial system of the kidneys was found to be distributed more widely throughout the renal vascular bed than in the control or other experiments (fig. 7).

*Experiment 9. Effect of Hypertensin.*—Twelve rabbits received varying amounts of hypertensin by intravenous injection. They were injected with ink and sacrificed during the following periods: (1) while the blood pressure was still rising, (2) at the height of the rise of the blood pressure, and (3) during the period in which the pressure was falling.

*Result:* In none of these animals was any anatomic indication of a "medullary by-pass" found. All of the cortical glomeruli were well filled with ink.

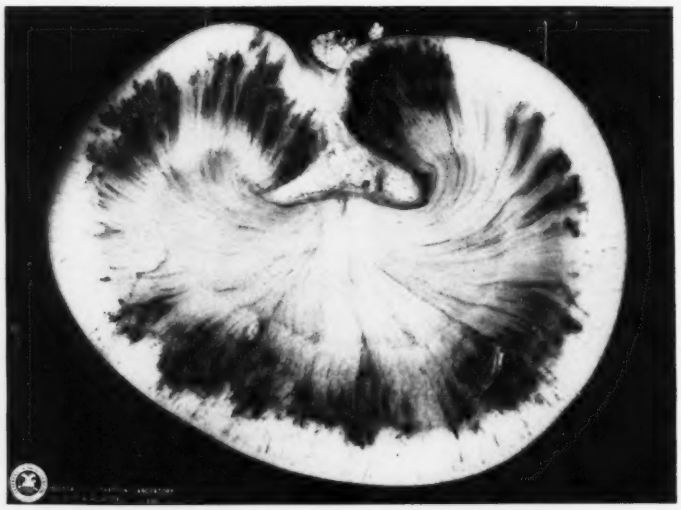

FIG. 6.—Sagital section of the kidney of a rabbit injected with ink during stimulation of the central end of severed sciatic nerve (X3).

FIG. 7.—Appearance of the cortex and medulla after ink injection at the time of the maximum rise of blood pressure following the administration of renin. Note the marked filling of the vasa recta systems in the medulla and the prominent juxtamedullary glomeruli (×6).

The cortical intertubular capillary network was only moderately well filled with ink. The juxtamedullary glomeruli were prominent and large and their efferent arterioles were also well filled. The animals that received hypertensin differed from all the other groups in that the ink in the glomeruli was more concentrated. If the renal vein was not ligated immediately after the injection of the ink, the intertubular capillaries of the cortex and vasa recta system in the medulla began to clear, while the glomeruli remained well filled and contrasted markedly with the poorly filled intertubular capillaries of the cortex. This latter observation suggests that there is constriction of the efferent arterioles of the glomeruli after the administration of hypertensin. This is consistent with the finding of Corcoran and Page[4] that the intracortical glomeruli as well as the cortical intertubular capillary network were ink-filled. In the 3 rabbits in which at least a part of the superficial cortex was not filled it is difficult to interpret of what importance, if any, was the exclusion of this portion of the cortex from the renal circulation, since it occurred only during stimulation of the nerve.

It is our opinion that vasoconstriction in the distal portions of the arcuate arteries resulted in the exclusion of the ink from the cortex supplied by the interlobular arteries arising from this portion of these vessels. Blood continued

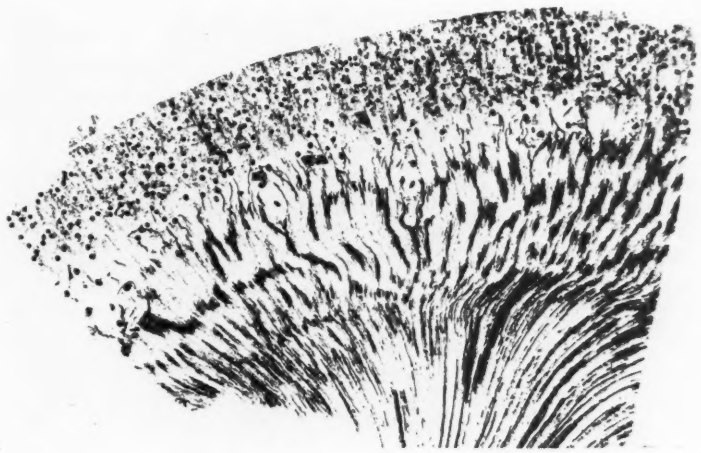

FIG. 8.—Appearance of the cortex and medulla following ink injection at the time of the maximum rise of blood pressure after the injection of hypertensin. Note the prominence of the ink-filled glomeruli (×8).

jection of hypertensin produces a rise in the glomerular filtration fraction (fig. 8). The marked concentration of ink in the glomeruli occurred also in the rabbits that received renin and were sacrificed during the period in which the blood pressure was rising.

## DISCUSSION

The results which we obtained, with the exception of those in some of the animals in the group in which the proximal end of the severed sciatic nerve was stimulated, were not in agreement with the reports of Trueta and collaborators. In none of the animals was the existence of a true "medullary by-pass" demonstrated. In most of the animals the superficial and deep to flow only through the most proximal portions of the arcuate arteries and the interlobular branches arising from these segments. There is, presumably, a marked drop in the arterial pressure distal to the constricted portion of the arteries, so that only the first portions of the interlobular arteries and the glomeruli which arise from them are perfused with blood. We think that this is the explanation of this phenomenon, rather than the so-called "medullary by-pass" offered by Trueta and associates.

A frequent observation, both in the control group as well as in the experimental animals, was the existence of small, patchy, ink-free

areas in the renal cortex. A few of these involved the whole width of the cortex, but the majority were composed of only the superficial, most peripheral glomeruli and subcapsular intertubular capillary network. In the latter instance, the distal portions of the interlobular veins in the areas containing no injected fluid were filled with ink. It is our opinion that the injected ink had already passed from the glomeruli and intertubular capillaries into the veins. In the first instance, in which the whole width of the cortex contained no injected fluid, we have found that these areas were supplied by the interlobular arteries arising from the first portion of the arcuate vessels. The ink, therefore, passed through this portion of the cortex first, and, when the kidneys were examined, it was found in the arcuate veins and the venous channels of the corticomedullary zones which drain these regions (fig. 9).

FIG. 9.—Appearance of the ink-filled interlobular veins of the cortex, the injected ink having already passed through the glomeruli and intertubular capillary network of the cortex (×4).

We think that the increased amount of ink in the venous channels which occurs during the administration of amyl nitrite is due to the rise in venous pressure which occurs simultaneously with the fall in the arterial pressure. The most significant effect of this drug on the renal circulation appears to be on the venous side, with marked dilatation of the cortical intertubular capillary network. The injected ink passes through the arterial side of the renal circulation into the dilated venous capillaries and is impeded in its flow from the interlobular and arcuate veins by the rise in venous pressure. Large amounts of the injected ink, therefore, collect in the venous components of the vasa recta, the venous channels in the juxtamedullary zone, and in the venous components of the cortical intertubular capillary network, and there may occur some retrograde flow of ink from the venous channels of the subcortical zone of the medulla into the interlobular veins in the cortex.

In the 4 animals in which amyl nitrite was administered and the renal vein cut, we think that the fall in arterial pressure resulted in the injected ink being carried through only the proximal portions of the "arcuate arteries" and the interlobular branches arising from these segments. Ink was present in the vascular bed of the deep zone of the cortex, between the patches of cortex that were ink-filled and those containing no injected fluid. The ink was found in the arcuate arteries, the proximal ends of the interlobular arteries, the glomeruli arising from these segments, the intertubular capillary network, and the juxtamedullary glomeruli and their efferent arterioles and the corresponding vasa recta in the medulla. There was no evidence of a "by-passing" of the cortex by the blood or injected material through a "medullary by-pass" produced by dilatation of the vessels associated with the juxtamedullary glomeruli.

## SUMMARY

1. We were unable to demonstrate the existence of two potential circulations in the kidneys of rabbits. No "medullary by-pass" or independent circulation through the medulla occurred.

2. From our observations it would appear that the arterial blood entering the kidneys through the renal arteries passes first through the cortex and then into the medulla.

3. In the kidneys of rabbits in which the blood pressure is elevated as a result of hyper-

tensin, and in which the blood pressure is rising following the injection of renin, there is a concentration of ink in the glomeruli. This observation suggests that there is constriction of the glomerular efferent arterioles.

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# Sustained Hypertension due to Pheochromocytoma

## Report of Case Cured by Removal of Tumor

*By* Hugh P. Smith, Jr., M.D., R. Bruce Logue, M.D., and Donald E. Beard, M.D.

Report of a case of sustained arterial hypertension due to an adrenal medullary tumor, excision of which resulted in return of the blood pressure to normal levels and relief of all symptoms. A brief discussion of the symptoms and signs and several useful diagnostic tests is included.

PHEOCHROMOCYTOMAS are tumors of special interest because they are capable of producing arterial hypertension, both of the paroxysmal and of the sustained type; furthermore, the hypertension they cause is one type that can be completely cured. Recognition of these tumors is of utmost importance since they can be completely relieved by surgical extirpation, and also because it is now known that pheochromocytomas are not as rare as formerly believed. The tumors have been known to pathologists since 1886, when Frankel[1] reported the autopsy findings of bilateral adrenal tumors and cardiac hypertrophy in a girl 18 years of age, who for three years had had attacks of palpitation, headaches, and vomiting. The clinical adrenosympathetic syndrome was first described in 1922 by Labbe, Tinel, and Doumer[2] and since then, pheochromocytomas have been recognized with increasing frequency. The first successful removal of such a tumor with cure of paroxysmal hypertension was reported in 1927 by Mayo.[3] A survey of the available literature now reveals that operations have been performed on at least 77 of these patients (including the present case), with death being reported in 16 cases.[4–14] Our case is one of sustained hypertension, with complete relief of symptoms following excision of a left adrenal medullary tumor.

### Case Report

The patient, a 23 year old, white man, first entered Emory University Hospital on October 23, 1947, complaining of headaches and weakness of his legs. These symptoms began in May, 1945, shortly after the patient had been rejected by the Army because of hypertension. He had passed the preinduction physical examination in January, 1945.

From the Departments of Medicine and Urology, Emory University School of Medicine, Emory University, Georgia.

Following their onset the headaches increased in severity. They usually occurred when the patient awakened in the mornings and improved during the day. They would recur for two or three days and then the patient would have none for several more days. Hot weather and physical exertion seemed to initiate them. The patient also noted episodes of weakness in his legs, with the attacks lasting one to three days. There was no numbness or dragging of his feet. He had mild palpitation occasionally. He also complained of nocturia three to ten times nightly without dysuria or daytime frequency. Pitting edema of his ankles which would clear up overnight was noted in January, 1947. At this time he was seen by a civilian physician, who noted a blood pressure of 260/130, a gland the size of a pecan in his left axilla, and a palpable spleen and liver. A diagnosis of malignant hypertension was made.

The symptoms became progressively worse until the patient was admitted to Emory University Hospital.

On admission, the blood pressure in the patient's right arm was 240/124; in his left arm, it was 260 plus/120; and in his right leg, 260 plus/150. Physical examination revealed no abnormality except for extreme constriction of the retinal arterioles without hemorrhages or exudates, a slightly enlarged heart with a Grade 1 systolic murmur at the apex, and frequent extrasystoles. The liver and spleen were not palpable. The left testicle was undescended.

The blood count revealed 4,750,000 red blood cells per cu. mm. with 15.9 grams (103 per cent) of hemoglobin, and 17,800 white blood cells with 4 per cent band forms, 68 per cent segmented polymorphonuclear neutrophiles, 8 per cent eosinophiles, and 20 per cent lymphocytes. On fourteen urine examinations the specific gravity varied between 1.002 and 1.012. There were three to twenty pus cells per high-powered field. On October 25, a trace of sugar was noted. The urinary output averaged 3,000 to 4,000 cc. daily.

An electrocardiogram showed left ventricular hypertrophy of the concordant type with frequent extrasystoles arising from multiple foci (fig. 1, *A*).

Amytal sedation lowered the blood pressure from 190/110 to 154/94. The cold pressor test showed practically no rise (fig. 2, *A*). Tetraethylammonium chloride caused no significant change in blood pressure. When 0.037 mg. of histamine base was given

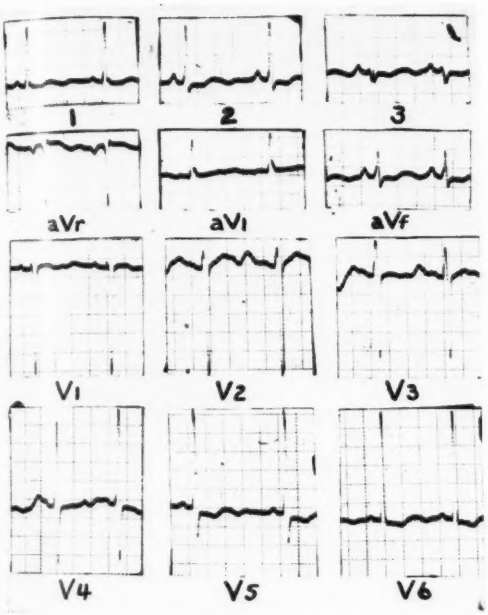


FIG. 1, *A*.—Electrocardiogram (before operation) showing left ventricular hypertrophy of the concordant type. The frequent ventricular extrasystoles are not illustrated.

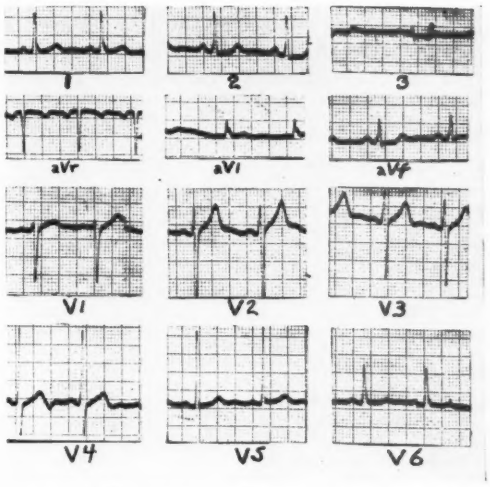


FIG. 1, *B*.—Electrocardiogram (after operation) showing disappearance of left ventricular hypertrophy pattern with return to sinus rhythm.

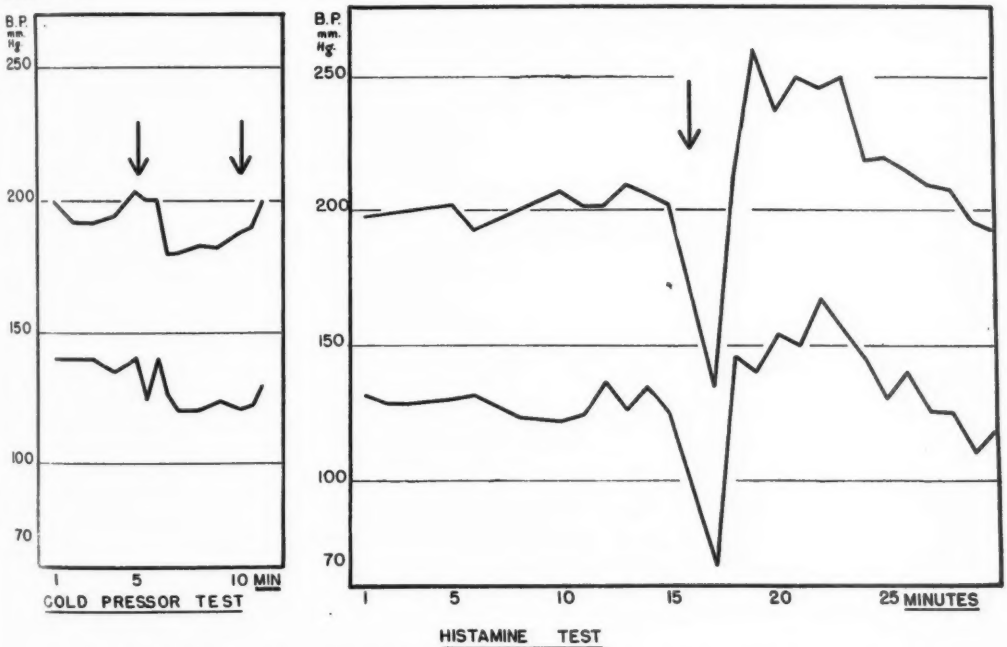


FIG. 2.—*Left:* The cold pressor test (before operation). Right hand immersed in ice water for sixty seconds at each of the arrows. *Right:* The histamine test (before operation). Time of intravenous injection shown by arrow.

intravenously, there was an immediate fall in blood pressure from 205/130 to 136/70, followed by a precipitous rise to 260/146, associated with a severe reaction with flushing, hyperventilation, numbness of the tongue, lips, and extremities, carpopedal spasm, and nausea (fig. 2, *B*). Massage over the adrenal areas failed to produce any attacks. Hyperventilation would easily produce headaches, carpopedal spasm, and a rise in blood pressure from 184/122 to 244/150. Intravenous urograms failed to reveal any deformity or evidence of a tumor.

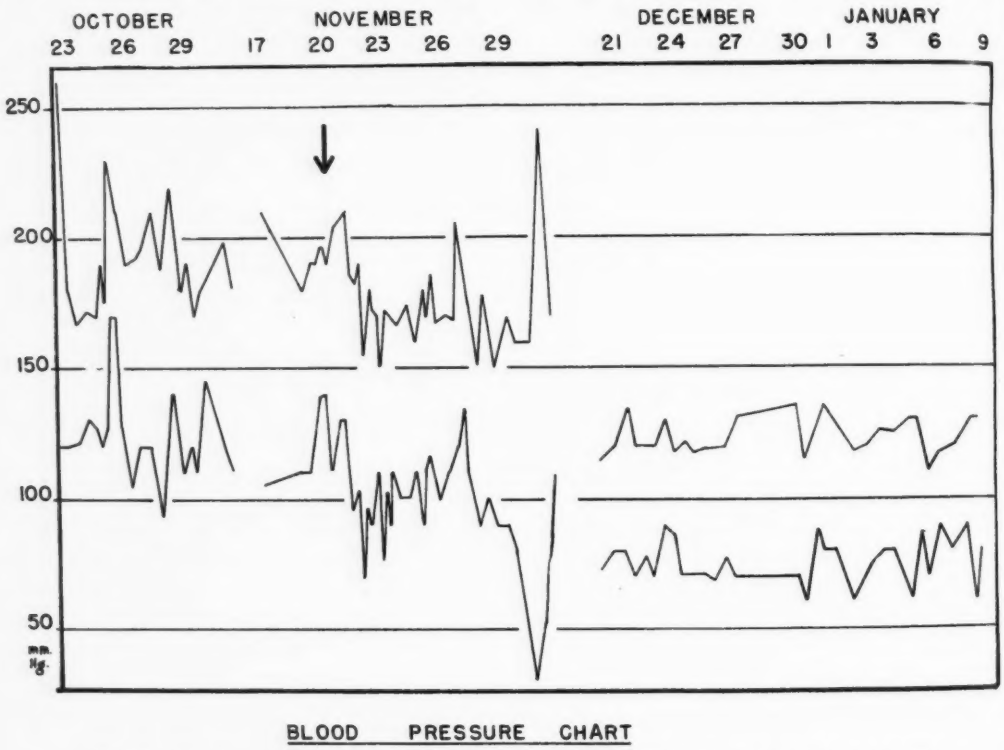


FIG. 3.—Blood pressure chart. Pheochromocytoma removed November 20, 1947 (arrow). Note delay in fall of pressure to normal.

Perirenal aerograms also failed to outline an adrenal mass.

On November 20, 1947, exploration of both adrenal glands through bilateral lumbar incisions revealed a normal right adrenal gland and a well-encapsulated tumor the size of a large egg in the left adrenal area. The tumor was completely excised. It measured 6.0 by 4.0 by 3.2 cm. and weighed 49 grams. No fluctuation in blood pressure occurred on the operating table. On November 22, a pericardial friction rub was noted. Serial electrocardiograms at this time showed no evidence of myocardial infarction or pericarditis. The patient's wound continued to drain but his fever subsided and he was sent home on December 2, 1947 (fig. 3).

The pathologist's report (concurred in by several examiners) was that the tumor was a malignant pheochromocytoma.

The patient returned to the hospital December 13, 1947, complaining of fever and pain in the left lower chest and left upper abdominal quadrant aggravated by deep inspiration. The left lumbar wound was still draining. A pleural friction rub was audible in the left axilla. A pericardial friction rub was again noted. The patient's temperature was 101.4 F. His pulse was 108, respirations 22, and blood pressure 160/95. X-ray examination revealed elevation of the left diaphragm, a tenting adhesion from the left diaphragm to the pericardium, and pneumonitis or atelectasis at the left lung base. An electrocardiogram showed changes compatible with acute pericarditis. A culture of the urine produced diphtheroids.

The fever slowly subsided under penicillin, streptomycin, and sulfadiazine therapy, but the pain and pericardial rub persisted and the signs of atelectasis and fluid remained at the left base

On December 21, the blood pressure was 120/80. The same day, 450 cc. of turbid, yellow fluid with a specific gravity of 1.020 was withdrawn from the left pleural space. Cultures of this fluid failed to produce any bacteria. The wound continued to drain. The pericardial rub was present intermittently. A blood culture failed to grow any bacteria.

On January 22, 1948, the left adrenal area was explored and about 1 oz. of unabsorbed oxycel gauze was found and removed. The patient responded well after this operation. His wound healed promptly. Reactions to the cold pressor and histamine tests were now negative (fig. 4). He was discharged on February 9, 1948, despite a persistent pericardial friction rub and low-grade fever.

A follow-up visit on June 21, 1948, (214 days after operation) showed the patient to be feeling well except for slight pain in his left chest on deep inspiration. The left wound still drained a small amount intermittently. However, he was back at work as a barber and had gained 23 pounds. His blood pressure was 140/80. The pericardial rub was no longer audible. The axillary node was smaller and was not tender. There was no evidence of metastasis. The electrocardiogram showed disappearance of the left ventricular hypertrophy pattern (fig. 1, *B*).

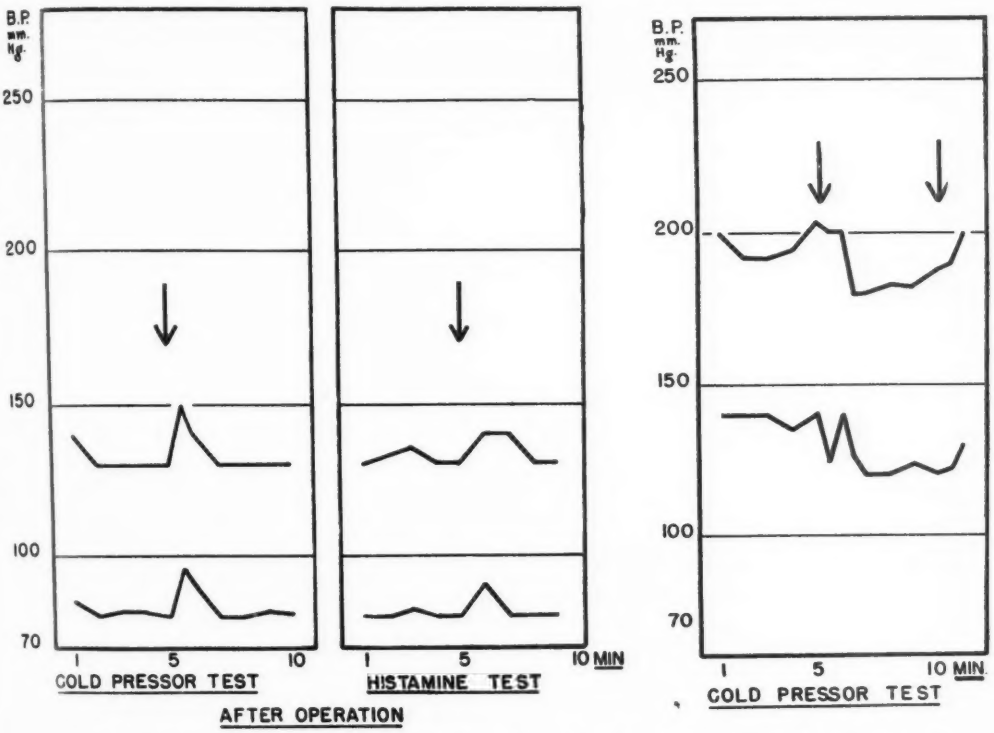


FIG. 4.—Cold pressor (before operation) and histamine tests (after operation). Reaction to histamine test has become negative.

## DISCUSSION

The incidence of pheochromocytoma is about equal in both sexes.[15] Most cases occur in persons between the ages of 20 and 50 years of age, but may occur in those of any age.[15] Neff and his associates[16] reported the successful removal of a pheochromocytoma from a 16 month old girl with hypertension and the adrenogenital syndrome.

The clinical attacks are the most impressive feature of the syndrome. They may vary in severity, frequency, and duration. They usually last for a few minutes to a few hours, but may occasionally last two or three days. There may be a history of attacks for several weeks or as long as sixteen years prior to diagnosis.[17] They usually increase in frequency, up to two or more

times a day; although there may be occasional remissions, lasting as long as ten years.[18] The attacks may occur at any time, but seem to have a predilection for the early morning.[19] Between attacks, the patient is usually healthy. At the onset of an attack, palpitation is common, with headaches and pain in the precordium or epigastrium. Nausea and vomiting are frequent. Anginoid pains, epigastric pain, roaring in the head, occipital headache, heat in the face, and sneezing are some of the other symptoms described.[20] Tachypnea is common. Pulmonary edema occurred at one time or another in 9 patients reported by Howard and Barker;[20] 3 of these died in their first attack. Palpitation, with a sense of vigorous heart action, either slow or fast, occurred in 95 per cent of their 18 cases and sweating in 78 per cent.[20] Vasomotor phenomena with pallor at first, usually followed by flushing and sweating, are common. There may be tremors. The pupils dilate. The neck veins may distend. Bauer and Belt[8] reported a case in a patient whose thyroid gland swelled with each attack. After the attacks there is intense prostration lasting from a few minutes to a day.

The blood pressure may be normal or elevated between attacks. In 51 cases reviewed by Green in 1946, only 14 patients showed intermittent hypertension, while 37 had chronic hypertension. During an attack, the blood pressure usually rises to extreme heights, usually over 260/120. In some cases, it has shown wavelike fluctuations at five- to fifteen-minute intervals.[15]

Hyperglycemia and glycosuria appear in about one-fourth of the cases. Albuminuria may be seen during an attack.

There is wide variation in the effect of pheochromocytomas on carbohydrate metabolism. Possibly in persons with the least stable carbohydrate homeostatic mechanism, overactivity of epinephrine from the tumor causes increased liver glycogenolysis. A prolonged hyperglycemia of nonpancreatic origin may lead to irreversible pancreatic islet-cell damage and diabetes. Two cases have been reported of typical diabetes mellitus cured by removal of an associated pheochromocytoma.[9,22] In these cases, permanent damage was shown by the retention of abnormal glucose tolerance curves, even though there was no longer hyperglycemia and no need for insulin after removal of the pheochromocytomas.

Other endocrine disorders have been reported in conjunction with pheochromocytomas. In the family reported by Calkins and Howard[23] as having multiple familial pheochromocytomas, there were 4 members with thyroid disease. These observers theorized that there might be some direct action on the thyroid by the secretion of the pheochromocytoma which induces nonsecretory thyroid enlargement, perhaps through its vascular effects. Certainly, thyroid enlargement and an elevation of the basal metabolic rate are not uncommon in persons with pheochromocytomas and may lead to a mistaken diagnosis of hyperthyroidism.[5,24] In another case of pheochromocytoma studied at Emory University Hospital and previously reported by Strickler,[19] the basal metabolic rate was +41 and +74 on two separate determinations.

There seems to be an unusually high incidence of associated generalized neurofibromatosis, this condition having been reported in nine cases of pheochromocytoma.[15]

Pheochromocytomas originate from the chromaffin tissue system. Chromaffin tissue is widely scattered in the body. Tumors have been reported arising from the intrathoracic sympathetic chain, from below the bifurcation of the aorta (organ of Zuckerkandl), from the coccygeal body, from the carotid body, and in the wall of the intestine, but none of these has produced the cardiovascular picture. Only those in the adrenal glands or in the retroperitoneal tissue between the kidneys have shown associated hypertension.[15]

Pheochromocytomas of all sizes have been reported, varying from a few centimeters to very large, melon-sized, cystic masses. In 15 cases the tumors have been bilateral in or near both adrenal glands, and in two other cases there have been simultaneous tumors in Zuckerkandl's body and in the retroperitoneal ganglia.[23] One-third of these cases were malignant, and, according to Calkins and Howard,[23] in none of these was there constant or paroxysmal hypertension. In the recent literature, how-

ever, there have been a few reports of patients with hypertension and malignant pheochromocytomas.[6, 7] The question of malignancy in pheochromocytomas is a difficult one to evaluate at present, because the histologic features usually denoting malignancy are a rather characteristic and diagnostic feature of the most benign pheochromocytomas.[25]

In 1942, there were 8 undoubtedly malignant cases with metastases reported among the 100 cases gathered by McGavack, Benjamin, Speer, and Klotz.[25] These metastasized widely to the regional lymph nodes, liver, bones, lungs, pleura, skin, intestines, and kidney, in that order of decreasing frequency.

The secretion from pheochromocytomas has usually been felt to be epinephrine. In 1937, Beer, King, and Prinzmetal[26] demonstrated a pressor substance in the blood during a hypertensive crisis, which they thought was epinephrine. However, actual proof of this fact is difficult. Demonstration of a pressor substance in the blood is not conclusive alone, for other substances may confuse the reactions, as in chronic lead poisoning and tuberculous destruction of only one adrenal gland.[8] Many persons have demonstrated that the excised pheochromocytoma contains a greatly increased amount of epinephrine over that encountered in the normal adrenal gland. In a recent case there were 2,300 mg. of epinephrine in a 350-gram tumor of the right adrenal gland.[13] The patient died on the operating table, and autopsy revealed two small pheochromocytomas of the left adrenal gland, as well as carcinoma of the thyroid gland with metastases from the thyroid tumor to lymph nodes in the cervical and paratracheal regions, again illustrating the somewhat tenuous connection between pheochromocytomas and thyroid abnormalities.

*Differential Diagnosis.* Paroxysmal hypertension has been reported with adrenal ganglioneuromas, with neuroblastomas, and with adrenal cortical tumors. Persistent hypertension has been found with retroperitoneal ganglioneuromas, with an adrenal sympathicoblastoma, and is not uncommon with adrenal cortical tumors.[15]

Paroxysmal hypertension can occur in: (1) pheochromocytomas, (2) essential hypertension, and (3) symptomatic hypertension. In essential hypertension, the blood pressure is always raised between attacks, the onset and end of attacks are gradual, convulsions and loss of consciousness are common, widespread symptoms are rare, and posture and pressure over the adrenal glands do not precipitate attacks. Symptomatic paroxysmal hypertension may be seen as recurrent attacks in lead poisoning, eclampsia, tabes dorsalis, aortic regurgitation, angina pectoris, thalamic tumors, nephritis, epilepsy, traumatic or vascular damage to the brain, meningitis, diseases of the gasserian ganglion, sciatic neuritis, infectious diseases, or allergy.[8, 15]

Since examination of the patient in an attack is so helpful in diagnosis, various methods of initiating attacks have been devised. Sometimes, attacks can be induced by hyperventilation, as in our case, or by massage over the adrenal area, or by changes in posture. The histamine test of Roth and Kvale is often used.[27] One-tenth of a cubic centimeter of histamine acid phosphate, 1:1,000, which is equivalent to 0.037 mg. of histamine base, may be given rapidly intravenously. In the normal person it usually produces little effect, but in the presence of a pheochromocytoma, it may cause a severe paroxysm of hypertension after the initial fall in blood pressure. In the present case, the reaction to the test was positive before removal of the pheochromocytoma and became negative after the successful excision of the tumor. Others have also confirmed the reliability of this test,[11] and still others have used the persistence of a positive reaction as evidence for the diagnosis of another tumor after removal of the first one, and have reoperated and removed a second tumor, following which the reaction has reverted to normal.[23] However, the histamine test is not specific for pheochromocytoma, but may also give a positive reaction in the presence of adrenal cortical tumors. We have recently observed a patient with sustained hypertension and a positive reaction to the histamine test (with coma and a rise in blood pressure from 210/130 to 290/165). At operation, no pheochromocytoma was found, but bilateral adrenal cortical adeno-

mas were found and removed. Following operation, the blood pressure fell to normal for two weeks then returned to 180/120, and the histamine reaction became negative.

Tetraethylammonium chloride has also been suggested as a test substance for pheochromocytoma.[28, 29] LaDue[28] observed a case with a positive reaction to the tetraethylammonium chloride test, but with negative reactions to benzodioxane and histamine tests.[28] In our case, tetraethylammonium chloride produced no symptoms or change in blood pressure. The adrenolytic benzodioxane drugs of the Fourneau series have been recommended recently as a test for hypertension due to circulating epinephrine.[30] These drugs should lower the blood pressure if it is elevated because of excessive circulating epinephrine. The test has been used in the Emory University Hospital with a dosage of 0.25 mg. of 933 F (piperidyl benzodioxane) per kilogram of body weight given intravenously in two minutes. It has been given to ten patients with hypertension without any untoward symptoms, but so far no fall in blood pressure has been produced and no pheochromocytomas have been found. In the case reported here operation was performed prior to the publication of the use of this test.

The subcutaneous injection of Mecholyl, 25 mg., has been suggested as a diagnostic test for pheochromocytoma.[14] Intravenous administration of 0.5 mg. of Mecholyl was tried in our above-mentioned patient with adrenal cortical adenomas, prior to publication of the article by Guarneri and Evans.[14] Although this caused an abrupt fall in blood pressure, lower than that caused by histamine, there was no succeeding hypertension, suggesting that the histamine-produced hypertension is not a compensatory rebound to a sudden hypotension.

The treatment of pheochromocytoma is surgical excision. Operation is not without danger. There is an increased susceptibility to paroxysmal tachycardias and to auricular or ventricular fibrillation in the presence of excess epinephrine. This may be one cause of death on the operating table. The patients often show a great rise in blood pressure when the tumor is being manipulated and a great fall in pressure after the veins from the tumor are ligated. For this reason, adequate amounts of epinephrine and adrenal cortical extract should be available prior to beginning the operation, and effort should be made to handle the tumor gently while removing it. It is possible that the benzodioxane drugs might be used to prevent excessive rises in blood pressure due to manipulation of the tumor at operation. Some have recommended preoperative cortical extract and extra salt feedings before operation to guard against acute adrenocortical insufficiency.[11] Arterial transfusions may help in avoiding the sudden vascular collapse. This collapse may be analagous to that seen during the operation for coarctation of the aorta when the clamps are too rapidly released. It has been suggested that this is due to splanchnic pooling with cardiac failure associated with diminished venous return.[31] In the case of pheochromocytoma, the generalized constriction of the vascular bed due to epinephrine is followed by generalized dilatation when the source of epinephrine is suddenly removed.

## Summary and Conclusions

A case report of a patient with sustained hypertension due to a pheochromocytoma of the adrenal gland is presented. The symptoms disappeared and the blood pressure gradually returned to normal following removal of the tumor. The use of various tests in the diagnosis of the condition is discussed.

## Addendum

Since this paper was submitted for publication, the patient has remained in good health and his blood pressure has remained at normal levels. A local abscess formed in the region of the sinus tract. This was incised and drained in June, 1949. At this time his blood pressure was 132/74 in both arms. An enlarged and tender lymph node was still present in the left axilla.

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# ABSTRACTS

## ARRHYTHMIAS

**Phillips, E., and Levine, S. A.: Auricular Fibrillation without Other Evidence of Heart Disease.** Am. J. Med. **7:** 478 (Oct.), 1949.

A study was made of 84 patients with auricular fibrillation of unknown etiology who had no evidence of organic heart disease. Transient fibrillation was noted in 23 and permanent fibrillation in 61. Frank congestive failure was present in 7 patients and an additional 7 had latent heart failure. Palpitation was the most common symptom of those without failure whereas dyspnea, orthopnea, and an enlarged liver were present in the group with failure. In 20 patients without frank failure, seven foot heart films showed an average transverse cardiac diameter of 14.4 cm. during fibrillation and 14.3 cm. after reversion. In 4 cases of congestive failure the transverse diameter averaged 17.4 cm. during and 15.4 cm. after auricular fibrillation. Electrocardiographic studies showed slight prolongation of the P-R interval after reversion in 6 patients. There was transient inversion of T waves after reversion in 4 patients. In 28 patients without failure the average vital capacity of the lungs was 3,448 cc. during auricular fibrillation and 3,700 cc. after reversion. The average vital capacity was 2,575 cc. before and 3,725 cc. after reversion in the group with heart failure. The arm to tongue circulation time averaged twenty-four seconds during auricular fibrillation and twenty seconds after reversion in 11 patients without failure. The venous pressure tended to be slightly elevated in those with some failure and returned to normal after treatment.

There was reversion to normal rhythm in 88.5 per cent of the patients following the use of quinidine. The normal rhythm persisted for an average of 26.9 months in those who relapsed. Nineteen have not relapsed and still have regular rhythm after a period lasting from two months to twenty-one years. In patients showing advanced congestive heart failure, symptoms and signs of heart failure disappeared after regularization.

It is concluded that auricular fibrillation may produce cardiac dilatation and congestive heart failure in patients with otherwise normal hearts. Regularization of the rhythm with quinidine in the early stages may prevent progressive heart failure and may be curative in the latter stages.

SCHWARTZ

## BLOOD COAGULATION

**Wise, W. D., Loker, F. F. and Brambel, C. E.: Effectiveness of Dicumarol Prophylaxis against Thromboembolic Complications following Major Surgery.** Surg., Gynec. & Obst., **88:** 486 (Apr.), 1949.

The efficacy of dicumarol in preventing postoperative vascular complications was studied in a series of 3,304 patients subjected to major surgical procedures. The therapy was begun on the second postoperative day. Comparison with a comparable untreated series of cases revealed a statistically significant reduction in the incidence of venous thrombosis in the patients receiving dicumarol prophylactically. However, it was pointed out that unless rigid standardization of laboratory procedure for gauging the dicumarol effect is continuously maintained, certain dangers are associated with carrying out such a program.

ABRAMSON

**Green, M. A. and Rosenthal, S.: Generalized Blood Platelet Thrombosis.** J. Mt. Sinai Hosp. **16:** 110, (Aug.), 1949.

Three cases of generalized blood platelet thrombosis are presented; the disease is an acute, fatal illness characterized by low grade fever, thrombocytopenia (including hemorrhagic manifestations), hemolytic anemia, and generalized or focal neurologic signs. The pathologic alterations consist of platelet thrombi in the arterioles and capillaries; these are distributed through the body but are found most commonly in the central nervous system, myocardium, renal cortex, adrenals and pancreas. In the central nervous system the thrombotic lesions are situated predominately within the cerebral cortex and a conspicuous feature is the mildness or complete absence of parenchymatous alterations.

The etiology of the syndrome is not known. A review of etiologic possibilities is discussed. The mechanism of the thrombotic phenomena is not understood.

LECKS

**Bigelow, W. G., Heimbecker, R. O., and Harrison, R. C.: Intravascular Agglutination (Sludged Blood), Vascular Stasis, and Sedimentation Rate of the Blood in Trauma.** Arch. Surg **59:** 66 (Sept.), 1949.

The authors attempted to study the subject of changes produced in blood by local trauma in the intact animal, utilizing a capillary microscope and colored motion pictures. The omentum and mesentery of both warm-blooded and cold-blooded animals were observed, using transilluminating light. Under normal conditions, the flow in all vessels was rapid and smooth. White blood cells were seen to occupy the periphery of the stream. The smaller capillaries allowed red cells to flow smoothly in single file without signs of clumping or rouleau formation being observed. When trauma was applied locally, definite changes occurred. First there was a slowing of the rate of flow, which caused a granular appearance in the larger venules and arteries. Then there was a movement of fluid and red blood cells from the vessels into the tissue spaces. White blood cells began to adhere and became fixed to the injured endothelium, particularly in the venous end of the capillaries. When resolution occurred, the first change was the appearance of pulsations in some of the blocked arteries, synchronous with the heart beat, and later the re-establishment of the movement of the blood. However, when this took place, clumps or aggregates of agglutinated cells passed into the general circulation. Several hours after the application of local trauma, red blood cells which exhibited no movement were noted in many arterioles, capillaries and venules in distal sites of the body. This reaction appeared to be due to blockage by the circulating agglutinated masses or sludge. Coincident with the healing of traumatized tissue, the circulation returned to its former state. The fate of the clumps of red blood cells could not be ascertained. Nor could the question of what produced their formation originally be answered on the basis of the available evidence.

ABRAMSON

**Rogers, J. F., Barrett, R. J. and Lam, C. R.: The Effect of Moderate Degrees of Dicumarol-induced Hypoprothrombinemia on Experimental Intravascular Thrombosis.** Surg., Gynec. & Obst. **89**: 339 (Sept.), 1949.

The effect of depression of the prothrombin level of blood with dicumarol on the production of experimental intravascular thrombosis was studied in a series of dogs. The drug was given in varying dosages in order to maintain the prothrombin activity at different levels, and then six veins in each animal were traumatized, in an attempt to produce thrombosis. Of the animals in which the prothrombin level fell to between 3 and 30 per cent of normal, the percentage of cases in which thrombosis occurred was only slightly below that observed in the control animals. Only in those instances in which the prothrombin level fell below 3 per cent of normal was thrombosis inhibited. However, in this group all animals demonstrated hematomas and 2 died of hemorrhage.

The authors conclude that a degree of dicumarol-induced hypoprothrombinemia, which is generally considered to be a desired therapeutic effect, does not significantly reduce the incidence of experimentally produced thrombosis.

ABRAMSON

**Quick, A. J., and Stefanini, M.: The State of Component A (Prothrombin) in Human Blood; Evidence That It Is Partly Free And Partly in an Inactive or Precursor Form.** J. Lab. & Clin. Med. **34**: 1203 (Sept.), 1949.

The formation of thrombin requires Component A (prothrombin), the labile factor, thromboplastin and combined calcium. None of the factors are accelerators. In fresh human plasma, Component A is present partly free and partly in an inactive or precursor state. Component A requires a rough surface for its activation, but there is no evidence that calcium, thromboplastin or thrombin are necessary for its conversion to the active stage. In oxalated human plasma, nearly all of Component A is changed to the active form after twenty-four hours of storage, if it is left in contact with a rough surface such as glass.

In the coagulation of plasma in which there is a deficiency of available thromboplastin due either to a lack of thromboplastinogen as in hemophilia or to a removal of platelets, the concentration of free Component A is markedly increased because little of the original active form is consumed and additional active Component A is produced from the inactive precursor.

Two types of congenital hypoprothrombinemia are known in which a deficiency of Component A occurs. In one type, a true deficiency of both free and total Component A exists. In the second type, which is the more common and is hereditary, the concentration of total Component A is normal, but the amount of the free or active form is below normal. This suggests that an unknown mechanism regulates the ratio of active to total Component A.

The authors show that a large fraction of the total Component A is in an active form. It is possible that in recent studies the activation of Component A has been misinterpreted as an acceleration of the conversion of prothrombin to thrombin. The two stage method of measuring prothrombin determines total prothrombin (Component A), but does not distinguish between the free and inactive form. The one stage method determines the free or active Component A, and to determine the total, all of Component A must first be converted to the active state.

MINTZ

## CONGENITAL ANOMALIES

**Potts, W. J.: Surgical Treatment of Congenital Pulmonary Stenosis.** Ann. Surg. **130**: 342 (Sept.), 1949).

One hundred and eighty-one patients, whose ages ranged from 10 weeks to 17 years, were operated upon at the Children's Memorial Hospital. Surgery was refused to no child, regardless of condition, if it could be demonstrated that there was diminished blood flow to the lungs. Skillful anesthesia was particularly important with this group of patients. During operation oxygen was conserved in patients with severe cyanosis by lowering the body temperature. The surgical approach in all children above 2 years of age with pulmonary stenosis was through the left fourth intercostal space. If the arch of the aorta curved to the left, an aortic-pulmonary anastomosis was done. If the arch curved to the right, a subclavian-pulmonary anastomosis was done.

Postoperative complications and the causes of death are outlined and discussed. The overall mortality rate (twenty-three deaths in 181 patients) was 12.7 per cent. The mortality rate in patients upon whom anastomoses could be performed (sixteen deaths in 165 patients) was 9.7 per cent. The results in those patients who survived surgery were very satisfactory; however, too few years have passed to guess intelligently the future of these children.

BECK

**Stauffer, H. M.: The Conventional Roentgen Examination in Operable Congenital Heart Disease.** Radiology **53:** 488 (Oct.), 1949.

The author presents the roentgenographic findings in Fallot's tetralogy, right aortic arch, tricuspid atresia, persistent truncus arteriosus, Eisenmenger's complex, isolated pulmonic stenosis, patent ductus arteriosus, interatrial and interventricular septal defects, and in coarctation of the aorta.

He states that only 14 of 50 cases of tetralogy of Fallot had "sabot" shaped hearts, most had small hilar vessels, while 10 of the 50 had an increase in the size of vessels extending beyond the hila, which was interpreted as being caused by a collateral arterial supply. Only one of 12 cases of right aortic arch had a high crossing to the left with typical esophageal displacement anteriorly. Only 5 of the 90 cases with patent ductus arteriosus had no prominent pulmonary artery; 90 per cent had only moderate cardiac enlargement and 25 of the 90 had slight left auricular enlargement. Left auricular enlargement was present in interatrial septal defects when mitral stenosis (Lutembacher syndrome) was present.

SCHWEDEL

## CONGESTIVE HEART FAILURE

**Little, J. M.: A Unified Concept of Cardiac Failure** Am. J. Med. **7:** 207 (Aug.), 1949.

Data taken from the literature and subjected to statistical analysis has been used to analyze present concepts and support the author's unified concept of cardiac failure. On the basis of this study it is postulated that normally a decrease in the mixed venous partial pressure of oxygen in response to increased oxygen utilization or inadequate blood oxygen capacity probably serves as a stimulus which results in an increased cardiac output and a decreased venous capacity, the decreased venous capacity being due to venoconstriction. These effects may be brought about by reflex or humoral control or by a combination of both.

In the normal individual an increased oxygen demand, such as is provided by exercise, would result in a slight or moderate rise in the central venous or atrial pressure, depending upon the adequacy of the increased cardiac output in response to the decreased mixed venous partial pressure of oxygen. In spite of the decreased venous capacity there would be no increase in central venous pressure if the increase in cardiac output were entirely adequate. In cardiac failure, whether acute, congestive, or anemic heart failure, an inadequate response of the heart with unimpaired venoconstriction would result in a marked increase in venous or atrial pressure. This concept does not imply that a decrease in mixed venous partial pressure of oxygen with consequent venoconstriction, as in failure of oxygenation, would necessarily result in an elevated venous or atrial pressure. Both the decrease in venous capacity and the ability of the heart to increase its output would be the deciding factors.

SCHWARTZ

**Kaindl, F., Polzer, K. and Werner, G.: The Action Currents of the Sensory Cardiac Nerves in Experimental Cardiac Failure.** Arch. internat. de pharmacodyn. et de thérap. **80:** 69, (July 1), 1949.

In 25 cats and 6 dogs anesthetized with ether or chloralose, the action currents of the afferent fibers of the inferior cardiac nerves were analysed before and after the intravenous injection of barbiturates. Evipan (30–50 mg./Kg.) and Pernocton (20–40 mg./Kg.) were injected with the intention of causing "cardiac failure". The number of the afferent impulses was found to be reduced after the injection of barbiturates. The authors conclude that barbiturates cause a paralysis of the receptors in the ventricular wall. This effect is spontaneously reversible but the recovery is accelerated by the injection of 0.05–1.0 mg. of strophanthin. Since barbiturates act in the same way on the denervated heart, the paralysis of the receptors in the ventricles does not play any part in the mechanism of this type of heart failure.

SCHERF

**Mettier, S. R., Weaver, J. D. and McBride, A. F.: The Effect of Stasis of Blood in Varicose Veins on Erythrocyte Fragility, with Accompanying Studies Comparing Red Cells and Other Blood Ele-**

**nents with Cubital Vein Blood.** Blood **4**: 1033 Sept.), 1949.

The authors report their attempt to evaluate the effect of in vivo stasis in varicose veins as a possible mechanism for increasing red cell fragility. Although the degree of stasis in varicose veins is not known, it seems well-established that the movement of blood in varicosities is very sluggish. They studied red blood cells from the varicose veins of 20 patients who had no demonstrable hemolytic tendency or other blood dyscrasia.

Each patient stood quietly for a period of at least fifteen minutes. Blood was then drawn from a tortuous dilated superficial vein and immediately afterwards from the cubital vein, without the aid of a tourniquet. In each patient, the fragility fell within the normal range in both specimens. A small but significant increase in red blood cell count was found in the blood from the varicose veins. This was felt to indicate a minor degree of hemoconcentration. The packed cell volume was only slightly higher in the blood from varicose veins than in cubital blood. If there had been some red cell swelling, one would have expected a greater increase. There was a suggestive increase in total serum proteins, but there was no significant difference in hemoglobin, platelets, or white cells.

The authors conclude that the theory that minor degrees of intravascular erythrostasis contribute substantially to some of the hemolytic anemias is untenable.

BEIZER

**Newman, E. V.: Function of the Kidney and Metabolic Changes in Cardiac Failure.** Am. J. Med. **7**: 490 (Oct.), 1949.

Studies were made of the mechanism of salt retention by the kidney by correlating the changes in renal function with the clinical and metabolic condition of a few intensively studied patients in cardiac failure, and also with the effect of stress and drugs upon the kidney in normal subjects and patients with cardiac failure. A simple correlation between the body sodium chloride balance and the renal circulatory pattern during recovery from congestive cardiac failure and edema was not found. It is suggested that the idea of a diminution in glomerular filtration rate as the primary reason for salt retention overlooks the possibility of metabolic, humoral or neurologic influences upon the renal tubular cells. Although reduction in the amount of glomerular filtrate presented to the renal tubules may occur in cardiac failure, the renal tubular cells are ultimately responsible for the regulation of output by selective reabsorption, allowing a small percentage of the filtered substances to escape into the urine. Antidiuretic and salt-retaining humoral substances may possibly be liberated and increase the renal tubular reabsorption of salt.

In addition, it may be demonstrated experimentally that exercise exerts a specific influence on sodium and chloride excretion and may represent in part the renal mechanism responsible for the edema in cardiac failure. The effect of mild exercise on patients with cardiac failure was investigated in regard to renal circulation and electrolyte excretion. A selective change in the excretion of sodium, chloride, and water occurred without significant change in potassium, phosphate or the glomerular filtration rate.

SCHWARTZ

**Harvey, R. M., Ferrer, M. I., Cathcart, R. T., Richards, D. W., Jr., and Cournand, A.: Some Effects of Digoxin upon the Heart and Circulation in Man.** Am. J. Med. **7**: 439 (Oct.), 1949.

Five patients with left sided heart failure who were studied by the cardiac catheterization procedure showed a similar early response to intravenous Digoxin. Before administration of Digoxin the pulmonary artery systolic, diastolic and mean pressures of all patients were elevated. The end diastolic pressures of the right ventricle, however, were normal; this was an indication of normal right auricular and peripheral venous pressure. The cardiac output was normal in one patient, low normal in another, and definitely reduced in the others. Peripheral resistance was increased in all, and blood volumes were increased to a variable extent in 4 patients. Following the injection of 1.0 to 1.5 mg. of Digoxin in 30 cc. of saline through the catheter into the pulmonary artery, the cardiac output and stroke volume rose and the pulmonary arterial pressure diminished without change in the right ventricular end diastolic pressure in all of these patients. The apical diastolic gallop found in 4 patients disappeared, the heart rate fell significantly in 2, and peripheral resistance was decreased in 4. A sixth patient with left ventricular failure showed similar changes in cardiac output, stroke volume, and pulmonary arterial pressure after the peripheral resistance had been lowered by quinidine.

It is pointed out that the increased stroke volume and the reduction in the pulmonary hypertension in the first 5 patients suggests a more adequate emptying of the left ventricle and a reduction in the residual blood volume of the left ventricle and left auricle. The increased systemic flow resulted in an increased return of blood to the right heart without detectable change in the end diastolic pressure of the right ventricle; this was the response of a normally functioning right heart in which large volume changes are associated with minimal filling pressure increase. In the patient treated with quinidine the production of peripheral vasodilatation enabled the left ventricle to empty more completely, thus reducing the pressures in the lesser circulation, and showing the importance of left ventricular action upon the pulmonary circulation. In the patient with chronic cor pulmonale, the right heart, working

against a reduced caliber and increased resistance of the pulmonary arterioles, was failing to empty itself as shown by the increase in end diastolic pressure. After Digoxin, better emptying of the right ventricle reduced the residual volume and filling pressure but caused the increase in the pulmonary artery systolic pressure.

On the basis of the hemodynamic changes noted in these patients for a short period after drug administration it is suggested that in cases of left ventricular failure Digoxin has a predominantly myocardial effect rather than an action upon the systemic venous system. Changes in peripheral vascular resistance after Digoxin probably represent reflex alterations in dynamics secondary to the increase in stroke volume rather than a primary effect upon the arterioles.

SCHWARTZ

## CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

**Bourne, W. A.: Acute Pericarditis Simulating Cardiac Infarction.** Brit. M. J., No. 4627: 579 (Sept. 10), 1949.

The author reports 2 cases of acute pericarditis simulating cardiac infarction. A 63 year old man was diagnosed clinically as a case of temporal arteritis. Two months later, an electrocardiogram showed changes indicating acute pericarditis, with elevation and deformity of the RS-T segment in all leads. This returned practically to normal a fortnight later. A 37 year old man developed epigastric pain while driving his car. An electrocardiogram showed the changes of acute pericarditis, with elevation and deformity of the RS-T interval in the limb leads and chest leads $CR_1$ to $CR_7$, maximal in Lead II and $CR_3$. After a fortnight the heart was clinically normal, but there was still slight elevation of the R-T interval, maximal in Leads II and $CR_4$. Both cases were at some stage diagnosed clinically as cardiac infarction, but in neither did complete analysis substantiate this diagnosis. The author suggests pericardial infarction as the mechanism responsible for these changes.

BELLET

**Levy, H.: Traumatic Coronary Thrombosis with Myocardial Infarction.** Arch. Int. Med. **84:** 261 (Aug.), 1949.

The author presents a case of thrombosis of a coronary artery with consequent myocardial infarction which appeared to have been produced by a nonpenetrating injury which caused a contusion of the anterior wall of the chest. Both the myocardial infarct and the occluding thrombus found at necropsy were of a histologic age consistent with the thirteen-day period between the day of the accident and the day of death.

The mechanism of cardiac damage in such cases is clear. The force of the external violence is transmitted to the heart muscle which undergoes varying degrees of reaction depending on the intensity of the impact. While the dramatic evidences of shock, with collapse, air hunger and pallor, may be present, more often symptoms are less obvious and so unobtrusive that patients are allowed their usual activity, only to die suddenly from rupture of the heart during the period of softening of the contused muscle. It is frequently difficult to differentiate the pain arising in a contused chest wall from that having its origin in bruised cardiac muscle. A slight rise in temperature or an increased rate of sedimentation of the red blood cells may serve to indicate the presence of bruised muscle tissue. Electrocardiographic abnormalities may be transient, lasting but a few days. On many occasions, the electrocardiogram, normal a few hours after the accident, shows abnormalities twenty-four or forty-eight hours later. In the severer contusions, electrocardiographic abnormalities similar to those seen in coronary disease with occlusion may occur. The importance of repeated electrocardiograms in cases of trauma is emphasized.

BERNSTEIN

**Katz, L. N., Mills, G. Y., and Cisneros, F.: Survival after Recent Myocardial Infarction.** Arch. Int. Med. **84:** 305 (Aug.), 1949.

The authors present the results of their analysis of the long term prognosis in 507 cases of recent myocardial infarction. It was found that the mortality rate was greatest in the first two months and then for a time lessened progressively. The rate continued to be high for the first year and then remained fairly steady from the second to the fifth year. By the end of the fifth to the sixth year, 81 per cent of the patients were dead. About one-fourth of the patients died in the first two months, about one-half had died at the end of a year, about two-thirds at the end of the third year and approximately four-fifths had died at the end of five years. Of the 52 patients who died after the second month following infarction in whom the cause of death was known, 19 per cent died of heart failure, 6 per cent of pulmonary embolism, and 65 per cent of a new myocardial infarction. Hypertension on admission had no effect on the mortality rate in the first two months but caused a slight increase in the long-term mortality. The presence of angina at the time of admission and up to one month preceding admission had no deleterious effect on the immediate mortality in the first two months, but the average duration of life of those who died after two months was somewhat shortened. It was also found that heart failure affects unfavorably the immediate and long term prognosis of recent infarction. The presence of diabetes mellitus increased the mortality rate in the first two months, as well as the overall mortality rate. The absence of low voltage, he[illegible]t

block, ectopic rhythms and sinus tachycardia led to a much better immediate prognosis, but did not influence the long term prognosis. The immediate mortality rate was greater in women than in men, but after the first two months the rate was less for women than for men. Infarcts of the lateral wall had a lower mortality rate than an anterior or posterior infarct. After two months little difference was found in the mortality rate between the anterior or posterior wall infarction. The mortality rate was greater for the whole group when the electrocardiogram was classified as showing an atypical coronary pattern.

SIMON

**Evans, W.: Triple Heart Rhythm as a Sign of Cardiac Pain.** Lancet, **2**: 737 (Oct. 22), 1949.

The author reports a study of 285 patients with chest pain without either valvular disease or hypertension. The cardiac pain in these patients probably resulted from coronary artery disease. In 139 the electrocardiogram was physiologic and no abnormal physical signs were found. In 146 a subsequent electrocardiogram showed evidence of cardiac infarction. Forty-one of this group showed a characteristic triple heart rhythm on auscultation; it soon became apparent that triple heart rhythm in any patient with chest pain predicted the electrocardiogram identified with cardiac infarction. The triple heart rhythm in cardiac infarction results from the addition of the third heart sound (protodiastolic or summation gallop) and can easily be discovered by routine auscultation. The remaining 105 patients with infarction presented "dual heart rhythm."

Though the incidence of a low blood pressure was not significantly greater in patients with triple heart rhythm than in those with dual rhythm (7 per cent against 2 per cent), the proportion with a high normal blood pressure was small among patients with triple rhythm (5 per cent against 19 per cent). Cardiac enlargement was almost twice as common in patients with triple rhythm (65 per cent) as in patients with "dual rhythm." Heart failure was present in 49 per cent of patients with triple rhythm and in only 6 per cent of those with dual rhythm. Though triple rhythm was sometimes present without either, it was more likely to be found in cardiac infarction when heart enlargement and failure existed side by side.

The author concludes that the help obtained from triple heart rhythm in the diagnosis of cardiac infarction as the cause of chest pain should encourage the clinician to seek to determine its presence diligently.

BELLET

**Dack, S., Master, A. M., Horn, H., Grishman, A., and Field, L. E.: Acute Coronary Insufficiency due to Pulmonary Embolism.** Am. J. Med. **7**: 464 (Oct.) 1949.

A study of 41 consecutive fatal cases of pulmonary embolism confirmed by autopsy showed that acute coronary insufficiency is an important factor in determining the resultant electrocardiographic and myocardial effects. In only a minority of cases was the electrocardiographic pattern of acute cor pulmonale found: deep $S_1$ and $Q_3$, depressed RS-$T_1$, elevated RS-$T_3$, and inversion of $T_3$. The majority of the electrocardiographic changes were characteristic of acute coronary insufficiency: RS-T depression and T wave inversion in one or more leads, and often in all leads.

Whereas the classic cor pulmonale pattern was seen more often in patients with previously normal hearts, the electrocardiographic changes were usually those of coronary insufficiency when the electrocardiogram prior to the embolism was very abnormal. The development of the cor pulmonale pattern was less likely to occur in the presence of marked left axis deviation. Although right ventricular dilatation was not regularly associated with either the cor pulmonale or coronary insufficiency pattern, the latter was often noted in patients with marked dilatation of the chambers of the right side of the heart. This suggests that right ventricular strain and coronary insufficiency may occur simultaneously following massive pulmonary artery embolism. Gross or histologic changes indicative of myocardial necrosis or infarction resulting from acute coronary insufficiency were found in ten cases. The right ventricle was involved in only one case, emphasizing the greater deleterious effect of pulmonary embolism on the left ventricle. Acute myocardial changes were found in cases with electrocardiograms indicative of cor pulmonale as frequently as in cases with electrocardiographic signs of acute coronary insufficiency.

It is concluded that coronary insufficiency following pulmonary artery embolism is caused by diminished coronary blood flow and myocardial anoxia which result from systemic shock, right ventricular dilatation, anoxemia and possible reflex vasoconstriction.

SCHWARTZ

## ELECTROCARDIOGRAPHY

**Clerc, A., and Quincaud A.: The Electrical Complex of the Heart after Ablation of the Intraventricular Septum.** Compt. rend. Soc. de biol. **143**: 834 (June), 1949.

The heart of the dog was exsanguinated by ligature of the vena cavae and vena azygos, and part or the whole of the intraventricular septum was excised through a cut in the ventricular wall. With total extirpation, A-V dissociation was observed. In direct and indirect bipolar leads the QRS and T waves changed their direction. The contractility of the heart was not altered. With subtotal extirpation or removal of only the lower part of the septum, no change in the electrocardiogram was seen; this indicates that a "paraspecific" connection

of auricles and ventricles was not interrupted by the latter procedure.

PICK

**Zollner, S.: The Recognition of Right Heart Strain With Special Reference to Pulmonary Emphysema and the Value of the So called P Pulmonale.** Arch. Kreislaufforsch. **14:** 353 (June), 1949.

An early diagnosis of right heart strain may be difficult before the onset of right heart failure. An analysis of the pathophysiology and an evaluation of clinical, x-ray and electrocardiographic findings in cases of emphysema has shown that clinical findings are of more importance for the diagnosis than laboratory methods. The diagnostic value of P pulmonale is restricted. According to the author's experience its absence in the electrocardiogram does not exclude marked hypertrophy and/or dilatation of the right auricle. On the other hand, it may be found with a normal heart in vertical or intermediate position. It is significant only if it occurs together with signs of right ventricular hypertrophy or with a marked right axis shift of the ventricular complexes.

PICK

**Coblentz, B., Harvey, R. M., Ferrer, M. I., Cournand A., and Richards, D. W., Jr.: The Relationship between Electrical and Mechanical Events in the Cardiac Cycle of Man.** Brit. Heart J. **11:** 1 (July), 1949.

The relationship between the electrical and mechanical events in the cardiac cycle of man were studied by recording the blood pressure in the right auricle, right ventricle, pulmonary artery and brachial artery simultaneously with the electrocardiogram.

In adults with essentially normal circulation, (1) the average time interval between the beginning of the P wave and the beginning of auricular systole was 0.09 second in 16 cases. (2) The average time interval between the beginning of Q and the beginning of the right ventricular systole was 0.075 second in 30 cases. (3) The average time interval between the beginning of Q and the beginning of the pulmonary artery systole was 0.085 second. (4) The duration of isometric contraction of the right ventricle, determined by subtracting (3) from (2), was 0.013 second. This time was necessary to raise the pressure in the right ventricle from 3 mm Hg to 8 mm Hg. (5) The average time interval between the beginning of Q and the beginning of brachial artery systole was 0.160 second in 30 cases.

The authors also discuss in detail the relationship between mechanical and electrical events in the various clinical disorders of the heart beat, in bundle branch block and pulsus alternans.

SOLOFF

**Littmann, D.: Ventricular Strain and Ventricular Hypertrophy.** New England J. Med. **241:** 363 (Sept. 8), 1949.

The author attempts to define certain electrocardiographic patterns as pathognomonic of strain and others of hypertrophy. In uncomplicated strain of the right ventricle there are ST-segment depressions and T-wave inversions over the right precordium, whereas right ventricular hypertrophy produces, in addition, prominent QRS complexes over the right precordium. Left heart "strain" has now been largely replaced by "hypertrophy." This is present when the QRS complexes from the left side of the precordium ($V_5$ or $V_6$ or both) consist largely or entirely of R waves of unusual height and duration (greater than 27 mm. in height with intrinsic deflection of 0.04 second or more after the origin) or when the sum of S in $V_1$ and R in $V_5$ exceeds 35 mm. Commonly these changes are accompanied by depressed or sloping S-T segment and an inverted T wave in $V_5$ or $V_6$. The author suggests that left ventricular strain without hypertrophy is seen in electrocardiograms that fulfill the ST-segment and T-wave requirements without R or S waves of abnormal size; this may be reversible. Hypertrophy without strain is suggested by records with R and S waves of heroic proportions but with normal S-T segments and T waves.

GOSFIELD

## HYPERTENSION

**Gorman, W. F. and Wortis, S. B.: Psychosis due to Thiocyanate Treatment of Hypertension.** J. Nerv. & Mental Dis. **110:** 46 (July), 1949.

The authors report a case of a toxic psychosis due to the use of thiocyanates in the treatment of hypertension. A 65 year old man with generalized arteriosclerosis and a blood pressure of 210/120, was given elixir of potassium thiocyanate, 1 gram a day. After he had ingested a total of 15 grams of potassium thiocyanate in eight days, he became uncontrollable and umanageable. The cardiovascular status was unaffected by either the drug or the manic state. Following cessation of medication, his course in the hospital was characterized by gradual mental clearing and he was discharged, recovered, three weeks after admission.

The authors state that the psychosis following potassium thiocyanate is characterized by psychomotor agitation, manic-like in nature, as well as sensorial defects, visual and auditory hallucinations, and paranoid delusions. They emphasize that an organic psychosis in a hypertensive patient taking thiocyanate may be due to intoxication by this drug.

BELLET

**Davis, L., Tanturi, C., and Tarkington, J.: The Effect of Reduced Blood Flow to the Liver in Renal Hypertension.** Surg., Gynec. & Obst. **89:** 360 (Sept.), 1949.

According to the recent theories regarding the factors responsible for the production of hypertension, the liver plays an important role both in the

elaboration of hypertensinogen, the precursor of hypertension, and in the formation of a vasodepressor substance, the latter resulting from a reduced oxygen tension due to a lowered blood flow through this organ. The authors therefore considered it of importance to determine the effect of decreasing liver blood flow in dogs with experimental renal hypertension. In each of the 5 animals studied, a substantial reduction in systolic blood pressure occurred following the application of Goldblatt clamps to the portal vein at the entrance of the vessel into the liver and to the common hepatic artery.

ABRAMSON

**Friedman, S. M., and Friedman, C. L.: Observations on the Role of the Rat Kidney in Hypertension Caused by Desoxycorticosterone Acetate.** J. Exper. Med. **89:** 631 (June), 1949.

The authors report their attempt to elucidate the mechanism whereby desoxycorticosterone acetate (DCA) is capable of producing a rise in the blood pressure of a wide variety of species, including man. In earlier experiments, the authors had noted that the rise in blood pressure in the rat appeared to be independent of alterations in renal function as determined by the clearance of inulin and sodium para-aminohippurate, and that this rise considerably preceded the onset of renal ischemia. However, they also had noted that where renal function was undisturbed by DCA, kidney weight was increased. Apparently normal renal function was maintained only by hypertrophy.

In order to demonstrate the relation between blood pressure rise and kidney involvement, pellets of DCA were administered for fifty-one days to albino rats of the Sherman strain which also received 1 per cent saline as drinking water. Treatment was stopped in representative groups at twenty-five, thirty-seven, and fifty-one days. It was noted that both the elevation in blood pressure during treatment and its reversal when treatment was stopped were closely correlated with corresponding changes in renal mass. The process did not become irreversible during the time it was studied. After removal of both kidneys, an aggravation of the hypertension was observed in DCA treated animals, suggesting that the kidneys are actively concerned with the excretion and possible inactivation of the steroid.

SCHWARTZ

## PATHOLOGY

**More, R. H., Waugh, D., and Kobernick, S. D.: Cardiac Lesions Produced in Rabbits by Massive Injections of Bovine Serum Gamma Globulin.** J. Exper. Med. **89:** 555 (May), 1949.

The authors noted a high incidence of granulomatous lesions of the heart valves and valve rings in a series of experiments designed to study the lesions of glomerulonephritis produced in rabbits by repeated intravenous injections of bovine serum gamma globulin. A total of 17 rabbits were anaphylactically sensitized to the bovine gamma globulin. The existence of hypersensitivity in the tested animals was indicated by the presence of a positive Arthus reaction and precipitins in the blood. Focal granulomatous lesions were found in the valves and valve rings of 9 animals. Valve lesions were present in 8 animals, lesions of the valve rings were present in 4 animals, and lesions in both locations were present in 3 animals. In addition, an arteritis was seen in the hearts of 2 animals. No similar lesions were present in 7 controls, 4 of which were injected with normal saline equivalent in volume to the dose of globulin administered to the treated animals. Histologically the lesions were found to be similar to, but not identical with, the lesions of human rheumatic fever. It is suggested that the similarities between the experimental and human valve and valve ring lesions indicate they may have a similar pathogenesis.

SCHWARTZ

**Spühler, V O.. and Morandi, L.: Scleroderma and Its Relation to the Libman-Sacks Syndrome, Dermatomyositis, and Rheumatic Infections.** Helvet. med. acta **16:** 147 (May), 1949.

This communication concerns two cases of generalized scleroderma and Libman-Sacks syndrome. In both cases the onset took the form of the Raynaud's syndrome, in one case combined with polyarthritic symptoms. The disease in both cases thereafter assumed the course of grave diffuse scleroderma. In one case there was, simultaneously, the picture of dermatomyositis. The course of the disease was febrile and rapidly progressive. During the latter months of observation *Pyococcus aureus haemolyticus* was found in the blood.

In the first case the pathologic-anatomic finding was of an embolizing, atypical, verrucous endocarditis with pericarditis, fibrinoid degeneration and necrosis of the lobular arteries and arterioles of the kidneys, chronic glomerulo-nephrosis, and chronic interstitial pneumonia. In the second case multiple parietal thrombi were found in both cardiac chambers, with secondary anemic renal infarcts, pericarditis and pleuritis, and focal fibrosis of the skeletal muscles and the myocardium.

AUTHORS

**Larrabee, W. F., Parker, R. L., and Edwards, J. E.: Pathology of Intrapulmonary Arteries and Arterioles in Mitral Stenosis.** Proc. Staff Meet., Mayo Clin., **24:** 316 (June), 1949.

This study was undertaken primarily to determine the state of the pulmonary vessels in 20 selected cases of mitral stenosis. Of these, 15 cases showed a significant quantitative reduction in calibre of the pulmonary arterioles. In 10 of these 15 cases, medial hypertrophy and intimal fibrosis of the pulmonary

arteries and arterioles were present. In the other 5 cases, medial hypertrophy was the essential change in the smaller intrapulmonary arteries and arterioles.

It is felt that patients with either intimal fibrosis or medial scarring of the smaller pulmonary vessels would not be expected to benefit from an operation that would restore essentially normal function to the mitral valve. Contrariwise, in those cases in which the occlusive pulmonary vascular lesions are those of medial hypertrophy, the patient might be expected to benefit from such an operation. With removal of the barrier caused by mitral stenosis it is expected that the engorgement of the pulmonary capillaries and edema of the alveolar walls would likely disappear or be reduced in degree. However, no such beneficial effect would be expected in the other two changes of the alveolar membrane; namely, thickening of the basement membrane and thickening of the alveolar epithelium. It seems that the two latter changes, if present, would persist regardless of any successful operative procedure. Such a situation might result in continued dyspnea even after essentially normal function had been restored to the pulmonary circulation and strain on the right portion of the heart had been reduced.

In general, from pathologic evidence, it seems justifiable to state that although little or no benefit could be anticipated from an ideal operation on the mitral valve in certain cases of mitral stenosis, in certain other cases, even though structural changes were present in the lungs, enough benefit might be anticipated so that continued attempts to develop such an operation aimed at relieving mitral stenosis and restoring essentially normal valvular function seem justifiable.

SIMON

**Altshuler, C. H., and Angevine, D. M.: Histochemical Studies on the Pathogenesis of Fibrinoid.** Am. J. Path. **25**: 1061, (Sept.), 1949.

The authors discuss the significance of fibrinoid degeneration of the connective tissue and report the results of their histochemical study of material derived from cases of rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, scleroderma, and other disease states featured by fibrinoid.

Fibrinoid, regardless of the etiologic factor, originated in the ground substance of connective tissue. It was closely associated with metachromasia and the presence of mucinous edema, all of these changes being noted in and around the Aschoff nodule and also in the nodules of rheumatoid arthritis. Metachromasia was apparently held in check in the early lesions of rheumatic fever by the action of the enzyme hyaluronidase. The older lesions were more resistant. This temporal relationship was also noted in rheumatoid arthritis and disseminated lupus. The authors note that fibrinoid contained considerable quantities of the amino acid, arginine. They state that the mucinous edema (of Talalajew) was associated with an increase in acid mucopolysaccharides; that the latter was precipitated from the ground substance of the connective tissue, forming or constituting "fibrinoid"; and that the precipitant was probably an alkaline protein substance, such as arginine, derived from necrosis of tissue.

GOULEY

## RHEUMATIC FEVER

**Fischel, E. E., and Pauli, R. H.: Serological Studies In Rheumatic Fever.** J. Exper. Med., **89**: 669 (June), 1949.

The authors report their attempt to repeat and extend previous investigations indicating the existence of allergic mechanisms in rheumatic fever. A substance called a "precipitinogen" had been reported previously in the serum of a rheumatic subject, following a sore throat, which precipitated when mixed with the serum taken during the subsequent rheumatic attack. This reaction has been called the "phase reaction" because the reaction occurred when serum obtained during Phase I or II (the sore throat and the latent period) was mixed with serum from Phase III (the period of rheumatic activity). It has been suggested that this precipitinogen might represent a secondary antigen derived from a combination of streptococcal products and human tissue constituents. Although the phenomenon did not necessarily represent an antigen-antibody reaction, it appeared to be one, and one intimately associated with the occurrence of rheumatic fever.

Studying 18 active rheumatic patients for long periods of time, the authors obtained negative, irregularly positive, and uniformly positive precipitin reactions. Positive precipitin tests were obtained with any combination of serum samples irrespective of their relationship to the phase of the disease. Many of the positively precipitating sera also showed positive reactions when mixed with control nonrheumatic sera. It is suggested that the "phase reaction" appears to be an inconstant phenomenon probably related to a colloidal abnormality of the serum, rather than to a specific antigen-antibody system.

In another series of experiments, using a complement fixation or collodion particle technic, no specific autoantibodies to human tissue extracts were demonstrable. The occurrence in rheumatic sera of agglutinins to collodion particles coated with a heart tissue extract was observed infrequently as compared with reactions to particles coated with extracts of other tissues. In addition, sera from syphilitic patients appeared to contain the agglutinins more frequently than did rheumatic sera. The possibility should be considered that autoantibodies are perhaps not specific for rheumatic fever but may be a type

of reaction similar to a biologically false positive Wassermann reaction.

SCHWARTZ

**Murphy, G. E., and Swift, H. F.: Induction of Cardiac Lesions, Closely Resembling Those Of Rheumatic Fever, in Rabbit Following Repeated Skin Infections With Group A Streptococci.** J. Exper. Med., **89:** 687 (June), 1949.

Cardiac lesions in rabbits, closely resembling those found in rheumatic fever, are described by the authors. After sustaining two to ten infections with streptococci of different serological types of Group A streptococci within three to twenty months, some rabbits sickened. Many recovered and a portion were sacrificed within ten to fourteen days following their last infection while exhibiting definite symptoms, leucocytosis, and elevated erythrocyte sedimentation rates. In several rabbits a severe illness developed following the last streptococcal infection and terminated fatally. Microscopic examination of the hearts of the successively infected rabbits which had sickened and succumbed, and of those sacrificed while sick, revealed focal alterations in the connective tissue framework in blood vessel adventitia, valves, mural endocardium, epicardium, and in the myocardial interstitium. Cardiac granulomata, which, in many respects, showed a histopathology strikingly similar to that of human rheumatic fever, were noted. Comparable lesions were not found in control rabbits.

In certain respects this experimental procedure of using multiple, successive infections with Group A streptococci follows the pattern encountered in rheumatic fever patients who have successive infections with different types of Group A streptococci. The carditis developed following infections with the same microorganisms that have been proven to occur in the infections that precede attacks of rheumatic fever in man. Among the random samples of rabbits subjected to the described experimental procedure, only a small portion developed these cardiac lesions. Similarly, only a small proportion of human subjects usually develop rheumatic heart disease. The authors feel it is justifiable to assume that similar host-streptococcus relationships may be operative and requisite in the pathogenesis of these cardiac lesions in rabbits and rheumatic carditis in man.

SCHWARTZ

## PHARMACOLOGY

**Jequier, R., and Plotka C.: The Synergistic Action of Oestradiol and Progesteron upon the Isolated Turtle Heart.** Compt. rend. Soc. de biol. **143:** 760 (June), 1949.

Oestradiol or progesteron, if acting alone, have no or only a slight effect on the isolated turtle heart. If acting simultaneously, however, they exert an effect similar to that of testosterone: a positive inotropic effect, a marked antagonism against acetyl choline, and inhibition of alternans produced by potassium. Thus, the combined action of these two hormones, indispensable to the functioning of the sexual organs, may also have an effect upon other organs, particularly the heart.

PICK

**Binet, L., and Burstein, M.: The Passage into the Circulation of a Vasodilatating Substance in the Course of Shock Produced in the Dog by Polyvinylpyrrolidone.** Compt. rend. Soc. de biol. **143:** 808 (June) ,1949.

Polyvinylpyrrolidone applied intravenously to the dog produces hypotension within the carotid artery and peripheral vasodilatation in a limb, even if its connections with the central nervous system are sectioned. This suggests the presence of a hormonal factor producing vasodilation; the nature of the hormonal factor remains to be determined.

PICK

**Walton, Robert P., and Brodie, Oliver J.: Cardiovascular Effects of Two Aliphatic Amines and of Ephedrine. I.** J. Pharmacol. & Exper. Therap. Part **96:** 343 (Aug.), 1949.

Two aliphatic amines, Aranthol (2-methylamino-6 hydroxy-6-methyl haptane) and Octin (6-methylamino-2 methyl-2-heptene) were studied by the authors and their cardiovascular effects compared with those of ephedrine. The purpose of the study was to attempt to find a drug capable of stimulating the myocardium which could be used in place of ephedrine in such conditions as orthostatic hypotension, hypotension following spinal anesthesia, and in special circumstances of sudden cardiac failure and arrest as is seen with general anesthesia.

The properties of Octin proved to be closely parallel to those of ephedrine but the drug appeared to have no distinctive value over ephedrine. Aranthol, on the other hand, when given in doses five and ten times greater than those producing comparable effects with ephedrine, showed some properties in animal experiments which seemed advantageous.

Aranthol increased contractility and also arterial pressure in the intact anesthetized dog in a fashion comparable to ephedrine. However, its margin of safety as measured by the difference between a stimulating dose and a dose large enough to depress the myocardium was tremendously greater than that of ephedrine. Its action when given subcutaneously could be prolonged by repeated dosage for 4 hours, and after the heart became refractory, further injections did not produce profound myocardial depression as occurred when ephedrine and Octin were given repeatedly. (The relative lack of myocardial depression after repeated dosage was confirmed in isolated rabbit heart preparations.) In the unanes-

thetized animal premature beats and irregular rhythms were produced. Seven patients received injections of Aranthol without any adverse effects.

GODFREY

**Mueller-Deham, A.: The Use of Digitalis in the Aged.** Geriatrics **4**: 303 (Sept.–Oct.), 1949.

In using digitalis in the aged, the outstanding considerations are: proper dosage, avoidance of side effects, and choice of the preparation. Three trends are open to question: the tendency to schematize the therapeutic dosage; its use for quick, full digitalization; and the modern preference for digitoxin. Individualization of dosage is necessary because the reaction and sensitivity of the abnormal heart to digitalis varies widely. Also, digitalis decreases the blood flow in healthy individuals and in some patients with heart disease. With quick and full digitalization, the possibility of severe, even dangerous, side effects is considerable. Digitoxin has the advantages of simple application, chemical purity and speedy effect, but it is the most toxic digitalis preparation.

Most authorities keep to the rule that during myocardial infarction due to coronary disease digitalis is in place only if congestive failure develops. However, when all the usual methods have been applied, and the patient, nevertheless, lies in immediate danger of death, an intravenous injection of one-fourth or one-fifth mg. of strophantin can be tried and eventually repeated. The author also states that a trial with cautious digitalization is justified whenever a diseased heart does not work optimally.

BELLET

**Levitan, B. A., and Scott, H. J.: Effect of Antihistaminics on Arrhythmias following Coronary Artery Ligation.** Canad. M.A.J. **61**: 306 (Sept.), 1949.

The antihistamine drugs, Pyribenzamine and Benadryl, were tested for their ability to inhibit the development of arrhythmias following coronary artery ligation. Dogs were anesthetized with sodium pentobarbital and a tracheal catheter was inserted. The circumflex branch of the left coronary artery was dissected free and looped at its origin. In Experiment A, the loop was tightened as soon as the corneal reflex returned and the chest was then sewed up with lungs inflated. In Experiment B, after the circumflex artery was loosely looped at its origin, the free ends of the ligature were led out of the chest at the ends of the incision and the chest was closed. On the day following the operation, the loop was tightened by traction on the free ends of the ligature.

Seven dogs in Experiment A served as controls and all succumbed after ligation of the circumflex artery. Electrocardiograms taken on three just before death showed ventricular fibrillation. After 7 dogs were given Benadryl intravenously in doses of 2 to 7 mg. per kilogram, the ligature about the circumflex artery was tightened. Only one dog survived. In 3 other dogs that received larger amounts of Benadryl, ventricular fibrillation occurred within ten minutes following ligation of the circumflex artery.

In Experiment B, 12 dogs were given 3 to 5 mg. per kilogram of Pyribenzamine on the day following the placing of the loose circumflex loop. The free ends of the loop were then pulled taut. Within twenty-four hours, 66 per cent died.

The authors concluded that although Pyribenzamine and Benadryl were unable to alter the mortality rates, they were able to a limited extent to suppress the appearance of ventricular extrasystoles.

BELLET

**Levitan, B. A., and Scott, H. J.: Inhibition of Chloroform-Adrenaline Fibrillation by Antihistaminics.** Canad. M.A.J. **61**: 303 (Sept.), 1949.

The authors endeavored to determine the possible antifibrillary activity of antihistaminics, since the feasibility of administering them by mouth might afford a wider clinical application than is possible with procaine. Dogs were anesthetized with sodium pentobarbital; a tracheal cannula was inserted and to this, a perforated tube was attached. Chloroform was administered for six-minute periods in a concentration which caused only a slight drop in blood pressure. After five minutes of chloroform, adrenaline, 0.02 mg. per kilogram, was injected intravenously as rapidly as possible. This procedure induced ventricular fibrillation. The antihistaminics Pyribenzamine or Antistine were given intravenously prior to, or in the same syringe as the adrenaline. The volume of the adrenaline solution varied from 1 to 5 cc. from animal to animal.

Four dogs used as controls all rapidly fibrillated following the injection of adrenaline. Pyribenzamine and Antistine when given simultaneously with adrenaline prevented the occurrence of ventricular fibrillation. This protection was inconstant and the effect of single doses usually lasted less than fifteen minutes.

The authors conclude that since procaine in doses of 5 mg. per kilogram has been reported to prevent chloroform-adrenaline fibrillation, with the effect lasting over an hour, it is apparent that the antifibrillary action of Pyribenzamine and Antistine is inferior to that of procaine. This suggests that the antifibrillary action of procaine is referable to some property in addition to the direct suppression of irritable foci in the myocardium. Since procaine blocks transmission across the superior cervical sympathetic ganglion of the cat, it is possible that part of the antifibrillary action of procaine resides in this ability to functionally interrupt the sympathetic pathway to the heart.

BELLET

**Blum, L., and Schneierson, S. S.: Intra-arterial Administration of Penicillin with Special Reference to Bone Marrow Concentration.** Surgery, 59: 176 (July), 1949.

Through the use of penicillin assays of bone marrow, the authors attempted to evaluate the efficacy of intra-arterial injection of this drug as compared with the intravenous and intramuscular routes. There was no consistent difference between the level of penicillin in the bone marrow after intravenous administration and the penicillin level after intra-arterial administration. However, a priming intravenous injection followed by a booster intra-arterial dose produced a considerably greater level of penicillin than that obtained after a single injection of the same total amount irrespective of the route of administration. Such an observation may have clinical significance with regard to infectious processes in bones.

ABRAMSON

**Stutzman, J. W., and Pettinga, F. L.: Mechanism of Cardiac Arrhythmias during Cyclopropane Anesthesia.** Anesthesiology 10: 374 (July), 1949.

In attempting to study experimentally the mechanism of cardiac arrhythmias produced by cyclopropane, the authors induced anesthesia in thirty-four normal unpremedicated cats with a mixture of cyclopropane and oxygen. Thirty minutes of this routine constituted a control experiment. The abnormal rhythms which began within a few minutes after induction consisted of ventricular premature contractions, ventricular rhythms with occasional supraventricular beats, bigeminal rhythm, and multiple-focus ventricular tachycardia at rates in excess of 250 per minute. As soon as a record of cardiac irregularities was obtained, partial abdominal evisceration, partial abdominal denervation, or bilateral adrenalectomy was performed. In a number of animals the abdominal viscera were subjected to traumatic manipulations. Since this did not abolish the arrhythmias, nonspecific trauma was ruled out as the cause of reversion to normal rhythm. Partial abdominal evisceration abolished the ventricular arrhythmias in five of seven cats. Bilateral adrenalectomy caused reversion to normal rhythm in one of the remaining two, and bilateral section of the sympathetic chain and splanchnicectomy at the tenth thoracic segment restored normal rhythm in the other.

On the basis of this work and that of Allen et al., it is concluded that cyclopropane increases the irritability of the cat's heart reflexly; afferent impulses from the mesentery or intestine are carried by fibers traveling with the splanchnic nerves; efferent impulses pass to the heart by way of the cardiac sympathetics; and endogenous epinephrine is necessary and adequate for the elicitation of spontaneous arrhythmias under these conditions.

BELLET

**Tamura, K., Kobayashi, Y., and Tokita, K.: A New Active Principle of Digitalis Purpurea and Lanata.** Japan. M. J. 1: 206 (June), 1948.

The present investigation was undertaken to ascertain the relationship between the cardiotonic activity and the toxicity of digitalis leaves. As a result of experiments on digitalis purpurea and lanata, the authors assume that in digitalis leaves there exist at least two substances which act on cardiac function, one having genuine cardiotonic action with low toxicity but extremely unstable, and the other a less active but more toxic action. There exists no strict parallelism between the two aspects of digitalis action. The cardiotonic potency of digitalis cannot be predicted solely from the results of toxicity tests, even though almost all methods of digitalis assay adopted at present by practically all pharmacopoeias of the world are only toxicity tests. On the basis of the divergence between the cardiotonic efficacy and toxicity, it is clear that the glycosides so far isolated are not the constituents that are responsible for the specific cardiotonic action but rather the toxic principles of the natural leaves. The authors were thus led to consider that an unknown substance exists in the leaves to which the specific improving effect upon blood circulation should be attributed.

Twenty Kg. of powdered leaves of digitalis purpurea were extracted with alcohol or ethylacetate and washed thoroughly with dried ether. The resulting substance was a brown powder, the yield being about 150 Gm. This new active glycoside named digicorin has low toxicity; high potency in exhibiting the cardiotonic action accompanied by a rise in the blood-pressure, in causing a distinct increase in the absolute force of the cardiac ventricle and in the minute-volume of the isolated frog heart; and a diuretic effect which is brought about with doses smaller than those necessary for the cardiotonic action.

BELLET

## PHYSICAL SIGNS

**Vesell, H.: Tricuspid Stenosis—A Simple Diagnostic Sign.** Am. J. Med. 7: 497 (Oct.), 1949.

The author describes a clinical sign which is simple to elicit and is indicative, if not pathognomonic, of tricuspid stenosis. In a case demonstrated at necropsy to have had tricuspid stenosis, a marked presystolic impulse was felt over the right jugular vein just above the clavicle and over the sternocleidomastoid muscle. This was of great force and was easily timed by comparison with the systolic aortic impulse in the episternal notch palpated by the index finger of the other hand. The strong presystolic venous impulse over the jugular vein was considered to be caused by the contraction of the hypertrophied right atrium. This impulse was readily transmitted to the neck because of the ob-

struction at the stenotic tricuspid orifice aided by the increased venous pressure and distention.

SCHWARTZ

**Cowen, E. D. H., and Parnum, D. H.: The Phonocardiography of Heart Murmurs. Part I. Apparatus and Technique.** Brit. Heart J. **11:** 356 (Oct.), 1949.

Because the standard instrument for phonocardiography was incapable of recording the majority of relatively high pitched systolic and diastolic murmurs, a new apparatus was constructed. The apparatus consists of a crystal microphone, a two-stage valve amplifier, and a Cambridge double-string Einthoven galvanometer. One fiber of this galvanometer is used for the electrocardiogram in the normal way; the other, which is used for the phonocardiogram, is tightened to its full extent in order to raise its high-frequency response. In this condition its sensitivity is about 1 mv./mm.

SOLOFF

**Cowan, E. D. H.: The Phonocardiography of Heart Murmurs. Part II. Clinical Results and Discussion.** Brit. Heart J. **11:** 360 (Oct.), 1949.

With the new instrument, the author tested the ability of phonocardiography (1) to distinguish an organic from an innocent systolic apical murmur in 57 cases of known congenital or valvular heart disease with systolic murmurs and twenty-seven cases with systolic murmurs without other evidence of disease; (2) to detect a presystolic murmur in 30 patients with mitral stenosis in whom only a systolic murmur was audible clinically; (3) to distinguish rheumatic from syphilitic aortic regurgitation in 11 cases of rheumatic origin, 5 of syphilitic and 5 of unknown etiology; (4) to detect aortic diastolic murmurs in hypertension when none was audible. Contrary to the experience of Evans, the phonocardiogram failed in all four attempts. The author believes that Evans' results are incorrect because his instrument was not satisfactory and because he used the electrocardiogram for timing. There is no strict correlation between electrical and mechanical events of the cardiac cycle.

SOLOFF

## PHYSIOLOGY

**Kottke, F. J., Koza, D. W., and Kubicek, W. G.: Studies of Deep Circulatory Response to Short Wave Diathermy and Microwave Diathermy in Man.** Arch. Phys. Med. **30:** 431 (July), 1949.

Seven experiments were conducted on young adult male subjects to compare the effects on renal circulation of heating with microwave diathermy with those observed when heating with short wave diathermy. The blood flow in the kidney was measured by clearance technic. Renal plasma flow and glomerular filtration were determined before, during, and after diathermy. The initial control plasma flow in all cases was in the normal range.

Circulatory adjustment during diathermy heating resulted in a decrease of renal plasma flow of 16 to 33 per cent. The filtration fraction showed an increase. There were no consistent changes in blood pressure. The effect on renal circulation with use of the Raytheon Microtherm was similar to that obtained with short wave diathermy. After heating was discontinued, the renal circulation slowly increased toward the initial level.

The authors state that this effect is not influenced by the location of the application of heat. Local intense heating in a circumscribed area of the surface of the body causes local vasodilation and increases local circulation. On the other hand, when large amounts of heat are applied to the body, cutaneous vasodilation occurs. The pulse rate and cardiac output increase and vasoconstriction occurs in the vascular beds not concerned with heat loss, such as the splanchnic and renal beds. Diathermy produces the latter type of effect (cutaneous vasodilation, etc.), initiating mechanisms to maintain internal hemostasis and resulting in vasomotor changes which cause vasoconstriction in the same area and which overshadow the vascular changes that increase circulation to the heated area.

BELLET

## SURGERY IN HEART AND IN VASCULAR SYSTEM

**Johnson, J., and Kirby, C. K.: An Experimental Study of Cardiac Massage.** Surgery **26:** 472 (Sept.), 1949.

Using the bubble meter to measure the blood flow through the thoracic aorta in dogs, the authors attempted to determine the rate of manual cardiac compression which would artificially maintain an efficient circulation.

It was found that up to a rate of 120 per minute, the rate of flow appeared to increase progressively as the rate of compression was increased. However, after fifteen or twenty minutes of cardiac massage, the blood flow in the thoracic aorta and carotid artery decreased significantly in most experiments. This followed a reduced venous return due to a diminished circulating blood volume.

The most effective technic of holding the heart for the purpose of cardiac massage appeared to be compression between one or more digits in front and one or more digits behind the heart. To maintain an adequate blood volume, the rapid intravenous administration of blood or physiologic saline solution was found to be of value. Furthermore cerebral blood flow could be enhanced by applying a non-crushing clamp intermittently to the thoracic aorta during the period of cardiac resuscitation.

ABRAMSON

**Miller, G. G., and Ripstein, C. B.: Resuscitation of the Surgical Patient.** Canad. M.A.J. **61:** 255 (Sept.), 1949.

The authors state that the causes of sudden collapse in the operating room fall into three groups. These are sudden decrease in the circulating blood volume, cardiac arrest, and respiratory failure. This paper presents a plan of action for dealing with such emergencies. The vital factors are maintenance of oxygenation by artificial respiration, restoration of cardiac action, and restoration of the blood volume.

To produce artificial respiration, an intratracheal tube is passed to establish a clear respiratory passage, and then inflation and deflation of the lungs is accomplished by mechanical means.

To restore the heart beat in cardiac standstill, one must stimulate the myocardium with adrenalin and cardiac massage. Heparin is of value in preventing thrombosis and keeping the blood fluid, and the tilt table has proved to be an effective method of aiding circulation. If adrenalin is used, the dose should not exceed 1 cc. of the 1:1000 solution and should be given into the right auricle. When ventricular fibrillation occurs, the first requisite is cardiac massage and artificial respiration to maintain an adequate circulation of oxygenated blood. The next step is the restoration of a coordinated heart beat. Procaine hydrochloride in a dosage of 5 to 10 cc. of a 1 per cent solution should be given intravenously or directly into the right auricle. In most instances, a second dose is necessary and must be followed by electrical stimulation.

To restore blood volume in massive hemorrhage with depletion of the circulating blood volume, the use of intra-arterial transfusion is advocated. Blood is introduced into the arterial tree in a central direction and thus the blood volume is quickly restored. Oxygenated blood is transfused into the radial artery under pressure at a rate of 150 to 200 cc. per minute.

BELLET

**Lowenberg, R. I., and Shumacker, H. B., Jr.: Experimental Studies in Vascular Repair. II. Strength of Arteries Repaired by End to End Suture, with Some Notes on Growth of Anastomosis in Young Animals.** Arch. Surg. **59:** 74 (July), 1949.

In an attempt to determine the strength of a sutured artery and the increase in circumference of the line of anastomosis during the period of body growth, the authors carried out a series of experiments in dogs, consisting of division and subsequent end to end suture of common carotid arteries.

It was found that the force necessary to break the recently sutured artery by direct pull was not great, but nevertheless such a vessel could withstand without leaking, intraluminal pressure far in excess of systolic blood pressure. The circumference of the artery at the line of anastomosis increased in size in the growing animal at a rate comparable to that observed in the unsutured portion of the vessel.

ABRAMSON

**Pierce, E. C., II., Rheinlander, H. F., Moritz, A. R., Gross, R. E., and Merrill, K., Jr.: Transplantation of Aortic Segments Fixed in 4 Per Cent Neutral Formalin. Report of Experiments in Dogs.** Am. J. Surg., **78:** 314 (Sept.), 1949.

The purpose of this study was to determine whether or not live tissue was necessary for establishment of satisfactory aortic grafts. Arterial segments preserved in 4 per cent neutral formalin were used in ten dogs for abdominal aortic grafts. There were no operative deaths in this series. Vascular channels of satisfactory size resulted in all experiments. There was one instance of suture disruption (secondary to infection). Dogs were kept as long as nine months after implantation of such aortic grafts. The grafts showed no tendency to dilate even under the stress of forced vigorous exercise. The most disturbing change that was observed in these grafts was degeneration of the media (fragmentation of elastica and calcification). The formalinized segment appeared to act as a framework, along which a new intima and adventia were laid down by the host.

The same type of preserved aortic segments were used to enter and join with the ventricle in sixty instances in the production of extracardiac shunts in dogs; 45 of these survived operation and were observed for short periods of time. There was no instance of thrombosis originating in the formalinized segment, nor was there any rupture or calcification in this series. In animals observed for sufficiently long periods of time firm union could always be demonstrated between the formalinized vessel and the ventricular wall.

On the basis of these preliminary experiments, it is believed that it may be possible to keep formalinized human aortic segments and use them in human subjects if circumstances demand the immediate bridging of an aortic gap and fresh tissue one is not available.

BECK

## THROMBOEMBOLIC PHENOMENA

**Robinson, L. S.: The Collateral Circulation Following Ligation of the Inferior Vena Cava.** Surgery **25:** 329 (Mar.), 1949.

In view of the recent trend to ligate the inferior vena cava below the renal veins for the treatment of deep venous thrombosis in the lower extremities, the author studied the collateral circulation that follows such a procedure. On the basis of an injection technic in stillborn infants, he found that seven groups of veins, which intercommunicate either directly or indirectly, are concerned with the estab-

lishment of the collateral circulation following ligation of the inferior vena cava. These are the vertebral plexus of veins; veins of the thoracic wall; veins of the neck; veins of the walls of the abdomen and pelvis; veins of the viscera of the abdomen and pelvis, including the portal system; veins of the thoracic viscera; and veins of the subcutaneous tissue of the abdomen and pelvis. The vertebral, azygos and portal system of veins are considered the most important routes.

It is concluded that with the inferior vena cava occluded, these collateral channels are more than adequate to return effectively the blood from the lower portion of the body to the heart without noticeable changes in the circulation.

ABRAMSON

**Warren, R., White, E. A., and Belcher C. D.: Venous Pressures in the Saphenous System in Normal, Varicose, and Postphlebitic Extremities.** Surgery **26**: 435 (Sept.), 1949.

Through direct canulization of one of the saphenous veins of the calf, the authors attempted to determine the changes in venous pressure produced by walking in a group of normal subjects, as compared with patients with varicosities or postphlebitic stasis. They found that the subject with a normal extremity could lower the pressure in the saphenous vein by walking; the one with varicosities could do this only half as well; while the patient with postphlebitic stasis was unable to reduce it at all. Occlusion of the saphenous vein resulted in a normal or even better than normal response in the case of the subject with uncomplicated saphenous varices, but this procedure did not affect the change observed in the postphlebitic limb. Superficial femoral vein ligation, when employed as a therapeutic procedure in the latter group, appeared to produce little improvement in venous function, as measured by the venous pressure determinations.

On the basis of their studies, the authors conclude that ligation of incompetent deep veins which have previously been damaged by disease does not particularly improve the existing condition. Furthermore, in many postphlebitic extremities, the saphenous veins, although prominent and slightly varicose, may serve a useful, though incomplete function. The test appears to give more accurate information with regard to the function of the deep system than tests which are dependent on visual or tactile estimations of venous filling.

ABRAMSON

**Cook, A. W., and Lyons, H. A.: Venous Thromboembolic Phenomena. Their Absence in Paraplegic and Tetraplegic Patients.** Am. J. M. Sc. **218**: 155 (Aug.), 1949.

In view of the fact that prolonged bed rest has been considered as an etiologic factor in the production of thromboembolic phenomena, the authors considered it of interest to study the incidence of such conditions in a group of patients whose extremities had not been moved for a long period of time because of injury to the spinal cord.

Although the patients in the group were subjected to relatively frequent surgical procedures, and although their lower extremities were almost constantly being exposed to the pressure of a bed or a wheel chair, none of them died from a pulmonary embolism.

The authors believe that the young average age of the patients in the series accounted for the absence of thromboembolic phenomena. In an attempt to explain this, they suggest that the basis for the influence of advancing age on the incidence of intravascular clotting may be, in part, the concomitant decrease in the human source of heparin, the mast cells.

ABRAMSON

## VASCULAR DISEASE

**Croom, J. H., and Scott, G. I.: Retinal and Vascular Damage in Long-standing Diabetes.** Lancet **1**: 555 (Apr. 2), 1949.

Sixty patients with long-standing diabetes (an average duration of eighteen and seven tenths years) were studied with regard to the changes in the retina. Of this number, 15 showed no evidence of degenerative disease, and in these no evidence of diabetic retinopathy or of arteriosclerotic change in the retinal vessels was present. Changes typical of diabetic retinopathy were noted in approximately one-third of the group. These consisted of characteristic hemorrhages or exudates and microscopic aneurysms. The hemorrhages were generally deeply situated, small, and roughly circular. The exudates were white and well defined and tended to be located nearer the macula than were the hemorrhages. Engorgement of the retinal veins was usually present but this was not pronounced. Arteriosclerotic changes in the vessels were minimal or absent.

The authors conclude that vascular and retinal complications are not inevitable in diabetes and that the retinopathy can develop in the absence of hypertension and general arteriosclerosis. Furthermore, there is no correlation between the severity of the diabetes or the control of the diabetic state and the development of cardiovascular complications.

ABRAMSON

**Duff, G. L. and McMillan, G. C.: The Effect of Alloxan Diabetes on Experimental Cholesterol Atherosclerosis in the Rabbit.** J. Exper. Med. **89**: 611 (June), 1949.

Cholesterol feeding in normal rabbits induced hypercholesterolemia of comparable degree to that produced by such feeding in rabbits rendered diabetic by alloxan. However, the atherosclerosis of the aorta in the diabetic animals was much less severe

than that in the normal rabbits. In addition there was an inhibition of the deposition of lipid substances in the liver, spleen, and adrenal glands of the diabetic rabbits. There was no gross or histological evidence of a morphological basis for this inhibitory effect. The only factors consistently associated with the inhibition of the expected morphologic effects of cholesterol feeding were the diabetic state and a degree of visible lipemia definitely greater than that seen in the controls.

The effect of alloxan diabetes on the retrogression of atherosclerotic lesions was studied in another series of experiments. There was no effect on retrogression within periods up to four months after the cessation of cholesterol feeding.

The authors conclude that the observed inhibitory effect depends upon an undetermined factor or factors connected with the diabetic state and that hypercholesterolemia is not the sole factor concerned in the development of experimental cholesterol atherosclerosis. The experiments indicate that the process of deposition of lipids in the arterial walls is influenced by factors different from those that are operative in the process of removal of lipids after they have been deposited. The inhibition of the development of experimental cholesterol atherosclerosis in alloxan diabetic rabbits depends on interference with the deposition of lipids and not on removal of lipids as fast as they are deposited.

SCHWARTZ

**McMaster, P. D., and Kruse, H.: Peripheral Vascular Reactions in Anaphylaxis of the Mouse.** J. Exper. Med. **89**: 583 (June), 1949.

The authors describe pronounced vascular changes occurring in the ears and claws of mice during anaphylactic shock. When a foreign serum enters the blood stream of sensitized animals marked local or generalized constriction of both arterial and venous vessels is noted almost at once. Although vascular spasm usually occurs simultaneously in both arteries and veins, it may appear first in the arteries or occasionally in the veins. The capillaries show no active constriction or dilatation but follow passively the changes in the larger vessels. The vascular changes, often not clearly seen grossly but quite evident under a low power of the microscope, appear not only in animals showing anaphylactic shock but also in many which present no other apparent signs of anaphylaxis. The vascular changes seem to constitute a sign of anaphylactic sensitivity far more delicate than the production of anaphylactic shock itself.

Peripheral vascular spasm occurs while carotid blood pressure is high. When the ear vessels begin to relax a few minutes later the carotid pressure remains high, but shortly thereafter there is a drop in blood pressure far below normal and the vessels remain open.

Vascular spasm does not occur in an ear if its circulation is obstructed during the production of anaphylactic shock. If the obstruction is released during the recovery period when the vessels in the other ear are dilated and blood pressure is very low, there is a resultant constriction of the vessels of the ear. The vascular reactions in the ears apparently are local in origin and are not a response to blood pressure changes in the large vessels or nervous stimuli.

SCHWARTZ

**Breu, W.: Hemoptysis in Heart Disease.** Arch. Kreislaufforsch. **14**: 291 (June), 1948.

Hemoptysis in heart disease occurs only if mitral stenosis is present. In the author's material it was observed in 6 per cent of all patients with involvement of more than one valve and in 10 per cent of cases with isolated mitral stenosis. No concomitant pulmonary disease, pulmonary infarction, or pulmonary edema was present in the cases selected for study. The hemorrhage had a sudden onset and was profuse (100–500 cc.). It was seen only in fully compensated cases, i.e., with unimpaired function of the right ventricle. The trigger mechanism for the hemoptysis appeared to be some toxic damage of the vascular wall of the pulmonary tree, usually following an infection.

PICK

**Bean, W. B., Cogswell, R., Dexter, M., and Embick, J. F.: Vascular Changes of the Skin in Pregnancy.** Surg., Gynec. & Obst. **77**: 739 (June), 1949.

The subject of vascular spiders and palmar erythema as banal complications of pregnancy was studied in a series of more than 1000 pregnant women. The vascular spider consists of a body, legs, and surrounding erythema. The temperature over a vascular spider is higher than that of the surrounding skin because of the local increase in arterial blood. The distribution is primarily over the upper parts of the body, with the face, neck, upper chest, and arms frequently affected. Palmar erythema occurs in two distinct forms in pregnant women. The first variety, which is similar to the "liver palms" of chronic hepatic disease, begins as a diffuse redness most prominent in the proximal part of the hypothenar eminence and later in the thenar eminence. Subsequently the parts of the palm between the metacarpo-phalangeal joints develop red spots and the palmar pads of the finger tips become red. The red areas are sharply separated from the neighboring normal skin. The other variety is an exaggeration of the normal mottling of the palm and it involves the entire palmar surface with a speckling of pale areas a millimeter or more in diameter.

In the present study vascular spiders were found in 66.6 per cent of all white women in the series and in 11.7 per cent of all Negro women at some time during pregnancy. Palmar erythema was observed in

62.5 per cent of white women and 35 per cent of Negro women. Both conditions occurred either alone or in association with the other. On the basis of data obtained from a number of liver function tests, the authors conclude that the vascular lesions in pregnancy are not caused by hepatic malfunction. They appear to be found frequently as accompaniments of normal pregnancy. The authors advance the hypothesis that these phenomena may be caused by hormones, possibly estrogenic substances.

ABRAMSON

**Cooper, F. W., Jr., Elkin, D. C., Shea, P. C., Jr., and Dennis, E. W.: The Study of Peripheral Vascular Disease with Radioactive Isotopes. Part II.** Surg., Gynec. & Obst. **88:** 711 (June), 1949.

The authors describe a method of studying peripheral vascular disorders by the use of radioactive sodium chloride injected into the muscle of an extremity. They studied the rate of removal of the material by means of an electromechanical device placed on the surface of the limb. This figure was found to be constant for any given individual. Patients with hyperthyroidism and hypertension demonstrated a rapid removal of the sodium, while in those with an advanced stage of thrombo-angiitis obliterans and arteriosclerosis obliterans, there was a retardation in the disappearance of the material. However, patients with a moderate degree of obliterative vascular disease still showed a normal rate of removal.

It is pointed out that in order to obtain constant results with this method, certain precautions must be taken. For example, the environmental temperature and the humidity must be rigidly controlled, the extremities must remain motionless during the entire procedure, the material must be injected a constant depth into the muscle, and, preferably, the extremities should be elevated. Apprehension will influence the readings significantly. All these factors affect the practicability of the method.

ABRAMSON

**Goetz, R. H., Ames, F.: Reflex Vasodilatation by Body Heating in Diagnosis of Peripheral Vascular Disorders.** Arch. Int. Med. **84:** 396 (Sept.), 1949.

The authors contend that reflex vasodilatation produced by body heating is the most practical, the most reliable, and the only method for diagnosis of peripheral vascular disorders not fraught with danger to the patient. Numerous other methods, including general anesthesia, spinal anesthesia, paravertebral block, the injection of typhoid bacilli or of sympathicolytic drugs, etc. are more difficult, more dangerous, and do not lend themselves to routine clinical examination, particularly in the patient's home. The method used in this study consisted of continuous recording of the peripheral circulation with the Goetz optical digital plethysmograph.

To obtain dilatation in the lower extremities, one arm was immersed in water to a point six inches above the elbow. The water temperature was kept constant at 45 C and vasodilatation was maintained for thirty minutes.

Vasodilatation could not be obtained when the circulation through the immersed extremity was interrupted; it was obtained in the upper extremities by immersion of the feet in the case of patients with high transverse spinal lesions (involving the sixth thoracic segment). Therefore, reflex vasodilatation is dependent on the return of heated blood, which acts on the thermosensitive center in the hypothalamus, and the mechanism of reflex vasodilatation from body heating is therefore not nervous in origin.

The pressure required for occlusion of the arterial circulation of the lower limbs by means of a cuff fixed on the thigh was considerably higher than that required for occlusion of the circulation to the hand with a cuff above the elbow. This fact frequently causes failure to keep the circulation through the lower limbs occluded and is considered the main reason why some investigators, having obtained reflex vasodilatation on immersion of a limb in which the circulation was thought to be occluded, have proposed a nervous reflex as the mechanism of vasodilatation.

BERNSTEIN

**Ambrose, A. M., and DeEds, F.: Further Observations on the Effect of Rutin And Related Compounds on Cutaneous Capillaries.** J. Pharmacol. & Exper. Therap. **97:** 115 (Sept.), 1949.

The exact mode of action of rutin on capillary permeability is not known. The best tentative explanation of rutin's ability to decrease the escape of trypan blue is that it has an antioxidant action toward epinephrine which permits a more prolonged action and actually higher blood levels of epinephrine. This in turn produces an increase in tonicity of the precapillary sphincters, a decrease in the total capillary bed, and therefore a decrease in the number of channels through which trypan can escape.

By using the trypan blue escape time on exposed irritated skin, the "rutin-like" action of compounds may be roughly assayed. Quercitrin, methyl hesperidin chalcone, sodium hespiridin chalcone and hesperidin acid phthalate were assayed by this method and all were found to have a distinct action in prolonging the trypan blue escape time.

GODFREY

**Goldman, M. L., and Schroeder, H. A.: Coarctation of the Aorta.** Am. J. Med. **7:** 454 (Oct.), 1949.

This report presents the combination of photo-electric plethysmography and direct measurement of arterial blood pressure as an aid in the diagnosis and location of coarctation of the aorta. Fourteen cases of coarctation of the aorta were studied using two photo-electric plethysmographs to compare si-

multaneously the relative blood flow in the ear lobes, fingers, scrotum or toes. A Hamilton optical manometer recorded direct arterial blood pressure simultaneously, as well as the contour of the pulse. It is pointed out that in severe coarctation the femoral pressure is often not obtainable by the auscultatory method, and in the less severe cases a falsely high femoral pressure may be recorded. Direct arterial puncture establishes the true value and makes possible the ready diagnosis of milder cases of coarctation. Confirmatory evidence is obtained with plethysmography.

In the cases studied by the authors there was evidence that both mechanical and humeral factors may operate to elevate blood pressure in coarctation. Thus, diastolic hypertension in the legs, which is usually accepted as evidence of generalized arteriolar constriction, was present in 2 patients. One of them showed a lesion just above the renal arteries. A low magnitude of the pulse similar to that seen in generalized hypertension which is evidence for generalized vasoconstriction, was present in 4 cases. On the other hand, the finding in 8 cases of a pulse wave in the upper part of the body higher than that seen in either patients with uncomplicated hypertension or in normal subjects was evidence for the presence of a mechanical factor.

It is concluded that the methods used in this study are an aid not only in locating the coarctation but also in evaluating the suitability of patients for surgery by determining the degree of coarctation and the extent of collateral circulation.

SCHWARTZ

**Steinberg, I., and Dotter, C. T.: The Differentiation of Mediastinal Tumour and Aneurysm: Value of Angiocardiography.** Brit. J. Radiol. **22:** 567 (Oct.), 1949.

The value of angiocardiography as an effective method for differentiating aneurysms from other space-occupying lesions of the thorax is illustrated by four cases: an extracardiac dermoid cyst with calcified margins simulating aneurysm of the ascending aorta; a saccular aneurysm with pulsation prevented by thrombus formation; an aneurysm of the descending aorta and a left lower lobe atelectasis produced by it; two aneurysms one of which was not filled probably because of its small orifice. Visualisation of the intact cardiovascular structures in patients with mediastinal masses rules out the presence of aneurysm, whereas opacification of a sacculated or fusiform structure is pathognomic of aneurysm. Rarely, aneurysms with narrowed channels or completely clotted lumina may not opacify. In such instances it may be helpful to find collateral evidence of aortic abnormality.

SCHWEDEL

**Kilmonth, J. B., Simeone, F. A., and Perlow, V.: Factors Affecting the Diameter of Large Arteries with Particular Reference to Traumatic Spasm.** Surgery **26:** 452 (Sept.), 1949.

The authors studied the subject of experimental traumatic spasm of large vessels, using the exposed femoral artery of rabbits or cats. It was found that spasm of the femoral artery produced by mechanical trauma to the vessel did not affect the limb volume of the paw unless the spasm extended sufficiently far along the artery to include the openings of branches. A rise in systemic blood pressure, regardless of the means utilized to produce the change, was attended by an increase in diameter of the femoral artery, while a fall resulted in a shrinkage in the vessel. These alterations occurred in the limb with the systemic nerves intact as well as in the limb with the sympathetic nerves removed.

The results did not support the concept that there was a nervous motor control of the large arteries. On the contrary it appeared that the caliber of these vessels followed passively the systemic blood pressure.

ABRAMSON

**Hill, E. J., Hammer, J. M., Saltzstein, H. C., and Benson, C. D.: Tetraethylammonium Chloride in Experimental Vascular Injuries of Limb, Bowel and Heart.** Arch. Surg. **59:** 527 (Sept.), 1949.

The authors attempted to determine whether establishment of collateral circulation following experimental injury to a major blood vessel would be enhanced by the use of tetraethylammonium chloride. For this purpose they ligated and sectioned the abdominal aorta in dogs and followed the clinical course in both untreated control animals and in animals receiving this drug. Another study was done to determine the effect of tetraethylammonium chloride on the mesenteric and coronary blood vessels.

After ligation of the abdominal aorta, most of the untreated dogs showed paralysis of the hindlegs and subsequently gangrene of the extremities. In the group of animals receiving the drug, there was a notable absence of paralysis, cyanosis and weakness of the limbs. All but 4 dogs showed no residual or immediate effects from ligation of the abdominal aorta. In the remaining cases, 2 showed gangrene and 2 died of conditions unrelated to the experiment. No favorable effect was observed from the administration of the drug in the case of ligation of the main stem mesenteric vessel; the same was true when the small vessels of the bowel were ligated. In fact, in the latter instance, the drug produced an unfavorable result.

It was concluded that tetraethylammonium chloride appears to be of value in certain injuries of peripheral vessels, but that it is not indicated for the removal of vasospasm in thrombosis of the mesenteric artery or in mechanical intestinal obstruction. Its use in involvement of the coronary arteries is questionable.

ABRAMSON

## OTHER SUBJECTS

**Hoobler, S. W., Malton, S. D., Ballantine, H. T., Jr., Cohen, S., Neligh, R. B., Peet, M. M., and Lyons, R. H.: Studies on Vasomotor Tone. I. The Effect of the Tetraethylammonium Ion on the Peripheral Blood Flow of Normal Subjects.** J. Clin. Investigation **28**: 638 (July), 1949.

Tetraethylammonium chloride (TEAC) blocks sympathetic and parasympathetic impulses at the autonomic ganglia. When 500 mg. were given intravenously it significantly increased the blood flow to the feet in normal subjects and produced vasodilatation in the hand in seven out of eight instances. Circulation in the forearm and calf was increased only slightly. Digital skin temperatures were increased. The compound did not produce vasodilatation after an extremity had been sympathectomized. Therefore, its vasodilator action is the result of the inhibition of sympathetic vasoconstrictor tone, and not the result of any direct action on the blood vessels. Since lumbar paravertebral block is about twice as effective as TEAC in increasing blood flow to the foot, the dosage of TEAC usually used may not cause complete sympathetic blockade. The increase in blood flow to the foot of normal subjects as a result of TEAC administration was much greater than that produced by aminophyllin, Papaverine, nicotinic acid, and nitroglycerin and slightly greater than the vasodilatation resulting from prolonged body heating. WAIFE

**Glenn, F., Keefer, E. B. C., Dotter, C. T., and Beal, J. M.: Observations on Experimental Aortic Anastomosis.** Proc. Soc. Exper. Biol. & Med. **71**: 619 (Aug.), 1949.

This report is based on observations made upon 3 dogs that were subjected to an end-to-end anastomosis of the thoracic aorta at the age of 6 weeks, and then studied approximately one year after operation by angiocardiography.

Femoral pulses were palpable in all 3 animals. The angiocardiographic studies revealed in each animal a definite narrowing at the site of the anastomosis. There was no evidence of compensating collateral circulation in any case.

One dog was subjected to thoracotomy 11 days after the angiocardiographic studies and the area of constriction was readily visualized. The diameter of the aorta appeared to be approximately the same above and below the site of stenosis. The lumen of the anastomotic site was larger than the lumen of the aorta had been when the dogs were 6 weeks of age.

These experiments revealed that although the dogs were under 5 pounds in weight and less than 8 weeks old at the time of operation, there were no technical mishaps as a result of the anastomosis. On the other hand, it appeared that the diameter of the lumen at the site of the anastomosis in these dogs did not keep pace in growth with the rest of the aorta. Therefore, possibly, the operation for coarctation should be deferred until the lumen is large enough in diameter to insure adequate size as the individual grows to maturity. MINTZ

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## TRAINING COURSE FOR CARDIOVASCULAR INVESTIGATORS

The training course for cardiovascular investigators, sponsored jointly by the American Heart Association, U. S. Public Health Service, and Western Reserve University School of Medicine, will be offered in the Department of Physiology for the second time, July 1, 1950–June 30, 1951. Professor C. J. Wiggers will be in personal charge. The course will consist of formalized training methods used in cardiovascular research, assisting experienced investigators with current research, independent research under supervision, and experience in the preparation of a manuscript.

Postdoctorate candidates accepted for training will be recommended to the U. S. Public Health Service for a research traineeship carrying a stipend ranging from $3,000 to $3,600 per annum, depending on the candidate's marital status. A maximum of ten trainees can be accepted.

For information and application blanks, address Dr. C. J. Wiggers, Program Director, Western Reserve University School of Medicine, Cleveland 6, Ohio.

## ELECTIONS HELD BY MEXICAN SOCIETY OF CARDIOLOGY

Dr Manuel Vaquero has been elected President of the Mexican Society of Cardiology. The other newly elected officers, who together with Dr. Vaquero make up the Board of Directors, are; Dr. Demetrio Sodi Pallares, Vice-President; Dr. Mario Vizcaino, Secretary, and Dr. Armando Cuellar, Treasurer.